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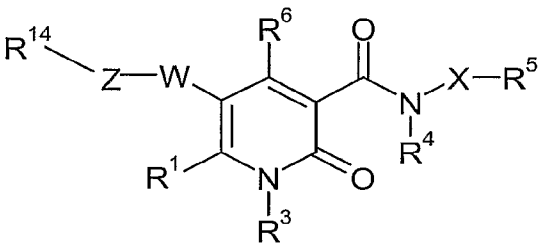
(54) Title: NOVEL COMPOUNDS II 2-PYRIDINE DERIVATIVES AS INHIBITORS OF NEUTROPHILE ELASTASE.



(57) Abstract: The invention provides compounds of formula wherein R^1, R^3, R^4, R^5, R^6, R^{14}, X, W and Z are as defined in the specification and optical isomers, racemates and tautomers thereof, and pharmaceutically acceptable salts thereof; together with processes for their preparation, pharmaceutical compositions containing them and their use in therapy. The compounds are inhibitors of human neutrophil elastase.

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Field of the Invention

The present invention relates to 2-pyridone derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

Background of the Invention

Elastases are possibly the most destructive enzymes in the body, having the ability to degrade virtually all connective tissue components. The uncontrolled proteolytic degradation by elastases has been implicated in a number of pathological conditions. Human neutrophil elastase (hNE), a member of the chymotrypsin superfamily of serine proteases is a 33-KDa enzyme stored in the azurophilic granules of the neutrophils. In neutrophils the concentration of NE exceeded 5 mM and its total cellular amount has been estimated to be up to 3 pg. Upon activation, NE is rapidly released from the granules into the extracellular space with some portion remaining bound to neutrophil plasma membrane (See Kawabat et al. 2002, Eur. J. Pharmacol. 451, 1-10). The main intracellular physiological function of NE is degradation of foreign organic molecules phagocytosed by neutrophils, whereas the main target for extracellular elastase is elastin (Janoff and Scherer, 1968, J. Exp. Med. 128, 1137-1155). NE is unique, as compared to other proteases (for example, proteinase 3) in that it has the ability to degrade almost all extracellular matrix and key plasma proteins (See Kawabat et al., 2002, Eur. J. Pharmacol. 451, 1-10). It degrades a wide range of extracellular matrix proteins such as elastin, Type 3 and type 4 collagens, laminin, fibronectin, cytokines, etc. (Ohbayashi, H., 2002, Expert Opin. Investig. Drugs, 11, 965-980). NE is a major common mediator of many pathological changes seen in chronic lung disease including epithelial damage (Stockley, R.A. 1994, Am. J. Resp. Crit. Care Med. 150, 109-113).

The destructive role of NE was solidified almost 40 years ago when Laurell and Eriksson reported an association of chronic airflow obstruction and emphysema with deficiency of serum α_1-antitrypsin (Laurell and Eriksson, 1963, Scand. J. Clin. Invest. 15, 132-140). Subsequently it was determined that α_1-antitrypsin is the most important endogenous inhibitor of human NE. The imbalance between human NE and endogenous antiprotease is

believed to cause excess human NE in pulmonary tissues which is considered as a major pathogenic factor in chronic obstructive pulmonary disease (COPD). The excessive human NE shows a prominent destructive profile and actively takes part in destroying the normal pulmonary structures, followed by the irreversible enlargement of the respiratory airspaces, as seen mainly in emphysema. There is an increase in neutrophil recruitment into the lungs which is associated with increased lung elastase burden and emphysema in α_1-proteinase inhibitor-deficient mice (Cavarra et al., 1996, Lab. Invest. 75, 273-280). Individuals with higher levels of the NE-α_1 protease inhibitor complex in bronchoalveolar lavage fluid show significantly accelerated decline in lung functions compared to those with lower levels (Betsuyaku et al. 2000, Respiration, 67, 261-267). Instillation of human NE via the trachea in rats causes lung haemorrhage, neutrophil accumulation during acute phase and emphysematous changes during chronic phase (Karaki et al., 2002, Am. J. Resp. Crit. Care Med., 166, 496-500). Studies have shown that the acute phase of pulmonary emphysema and pulmonary haemorrhage caused by NE in hamsters can be inhibited by pre-treatment with inhibitors of NE (Fujie et al.,1999, Inflamm. Res. 48, 160-167).

Neutrophil-predominant airway inflammation and mucus obstruction of the airways are major pathologic features of COPD, including cystic fibrosis and chronic bronchitis. NE impairs mucin production, leading to mucus obstruction of the airways. NE is reported to increase the expression of major respiratory mucin gene, MUC5AC (Fischer, B.M & Voynow, 2002, Am. J. Respir. Cell Biol., 26, 447-452). Aerosol administration of NE to guinea pigs produces extensive epithelial damage within 20 minutes of contact (Suzuki et al., 1996, Am. J. Resp. Crit. Care Med., 153, 1405-1411). Furthermore NE reduces the ciliary beat frequency of human respiratory epithelium *in vitro* (Smallman et al., 1984, Thorax, 39, 663-667) which is consistent with the reduced mucociliary clearance that is seen in COPD patients (Currie et al., 1984, Thorax, 42, 126-130). The instillation of NE into the airways leads to mucus gland hyperplasia in hamsters (Lucey et al., 1985, Am. Resp. Crit. Care Med., 132, 362-366). A role for NE is also implicated in mucus hypersecretion in asthma. In an allergen sensitised guinea pig acute asthma model an inhibitor of NE prevented goblet cell degranulation and mucus hypersecretion (Nadel et al., 1999, Eur. Resp. J., 13, 190-196).

NE has been also shown to play a role in the pathogenesis of pulmonary fibrosis. NE: α_1-protenase inhibitor complex is increased in serum of patients with pulmonary fibrosis, which correlates with the clinical parameters in these patients (Yamanouchi et al., 1998, Eur. Resp. J. 11, 120-125). In a murine model of human pulmonary fibrosis, a NE inhibitor reduced bleomycin-induced pulmonary fibrosis (Taooka et al., 1997, Am. J. Resp. Crit. Care Med., 156, 260-265). Furthermore investigators have shown that NE deficient mice are resistant to bleomycin-induced pulmonary fibrosis (Dunsmore et al., 2001, Chest, 120, 35S-36S). Plasma NE level was found to be elevated in patients who progressed to ARDS implicating the importance of NE in early ARDS disease pathogenesis. (Donnelly et al., 1995, Am. J. Res. Crit. Care Med., 151, 428-1433). The antiproteases and NE complexed with antiprotease are increased in lung cancer area (Marchandise et al., 1989, Eur. Resp. J. 2, 623-629). Recent studies have shown that polymorphism in the promoter region of the NE gene are associated with lung cancer development (Taniguchi et al., 2002, Clin. Cancer Res., 8, 1115-1120.

Acute lung injury caused by endotoxin in experimental animals is associated with elevated levels of NE (Kawabata, et al., 1999, Am. J. Resp. Crit. Care, 161, 2013-2018). Acute lung inflammation caused by intratracheal injection of lipopolysaccharide in mice has been shown to elevate the NE activity in bronchoalveolar lavage fluid which is significantly inhibited by a NE inhibitor (Fujie et al., 1999, Eur. J. Pharmacol., 374, 117-125; Yasui, et al., 1995, Eur. Resp. J., 8, 1293-1299). NE also plays an important role in the neutrophil-induced increase of pulmonary microvascular permeability observed in a model of acute lung injury caused by tumour necrosis factor α (TNFα) and phorbol myristate acetate (PMA) in isolated perfused rabbit lungs (Miyazaki et al., 1998, Am. J. Respir. Crit. Care Med., 157, 89-94).

A role for NE has also been suggested in monocrotoline-induced pulmonary vascular wall thickening and cardiac hypertrophy (Molteni et al., 1989, Biochemical Pharmacol. 38, 2411-2419). Serine elastase inhibitor reverses the monocrotaline-induced pulmonary hypertension and remodelling in rat pulmonary arteries (Cowan et al., 2000, Nature Medicine, 6, 698-702). Recent studies have shown that serine elastase, that is, NE or vascular elastase are important in cigarette smoke-induced muscularisation of small

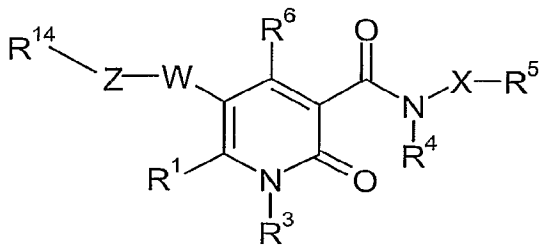
pulmonary arteries in guinea pigs (Wright et al., 2002, Am. J. Respir. Crit. Care Med., 166, 954-960).

NE plays a key role in experimental cerebral ischemic damage (Shimakura et al., 2000, Brain Research, 858, 55-60), ischemia-reperfusion lung injury (Kishima et al., 1998, Ann. Thorac. Surg. 65, 913-918) and myocardial ischemia in rat heart (Tiefenbacher et al., 1997, Eur. J. Physiol., 433, 563-570). Human NE levels in plasma are significantly increased above normal in inflammatory bowel diseases, for example, Crohn's disease and ulcerative colitis (Adeyemi et al., 1985, Gut, 26, 1306-1311). In addition NE has also been assumed to be involved in the pathogenesis of rheumatoid arthritis (Adeyemi et al., 1986, Rheumatol. Int., 6, 57). The development of collagen induced arthritis in mice is suppressed by a NE inhibitor (Kakimoto et al., 1995, Cellular Immunol. 165, 26-32).

Thus, human NE is known as one of the most destructive serine proteases and has been implicated in a variety of inflammatory diseases. The important endogenous inhibitor of human NE is α_1-antitrypsin. The imbalance between human NE and antiprotease is believed to give rise to an excess of human NE resulting in uncontrolled tissue destruction. The protease/ antiprotease balance may be upset by a decreased availability of α_1-antitrypsin either through inactivation by oxidants such as cigarette smoke, or as a result of genetic inability to produce sufficient serum levels. Human NE has been implicated in the promotion or exacerbation of a number of diseases such as pulmonary emphysema, pulmonary fibrosis, adult respiratory distress syndrome (ARDS), ischemia reperfusion injury, rheumatoid arthritis and pulmonary hypertension.

Disclosure of the Invention

In accordance with the present invention, there is therefore provided a compound of formula (I)



(I)

wherein

R^{1} represents hydrogen or C_1-C_6 alkyl;

W represents $S(O)_m$ wherein m represents an integer 0, 1 or 2;

Z represents a single bond, $-CH_2-$ or $-NR^{25}-$;

R^{14} represents a hydrogen atom or OH or a group selected from C_1-C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur; each group being optionally substituted with at least one substituent selected from phenyl, C_1-C_6 alkoxycarbonyl, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CN, OH, NO_2, C_1-C_3 alkyl substituted by one or more F atoms, C_1-C_3 alkoxy substituted by one or more F atoms, $NR^{12}R^{13}$, $C{\equiv}CR^{30}$, $CONR^{31}R^{32}$, CHO, C_2-C_4 alkanoyl, $S(O)_pR^{33}$ and OSO_2R^{34};

R^{12} and **R**^{13} independently represent H, C_1-C_6 alkyl, formyl or C_2-C_6 alkanoyl; or the group $-$**NR**^{12}**R**^{13} together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{26};

R^{30} represents H, C_1-C_3 alkyl, $Si(CH_3)_3$ or phenyl;

$\mathbf{R^{33}}$ and $\mathbf{R^{34}}$ independently represent H or C_1-C_3 alkyl; said alkyl being optionally substituted by one or more F atoms;

$\mathbf{R^6}$ represents H or F;

$\mathbf{R^3}$ represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said ring being optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, cyano, C_1-C_6 alkoxy, nitro, methylcarbonyl, $NR^{35}R^{36}$, C_1-C_3 alkyl substituted by one or more F atoms or C_1-C_3 alkoxy substituted by one or more F atoms;

$\mathbf{R^{35}}$ and $\mathbf{R^{36}}$ independently represent H or C_1-C_3 alkyl; said alkyl being optionally further substituted by one or more F atoms;

$\mathbf{R^4}$ represents hydrogen or C_1-C_6 alkyl optionally substituted with at least one substituent selected from fluoro, hydroxyl and C_1-C_6 alkoxy;

X represents a single bond, O, NR^{24} or a group -C_1-C_6 alkylene-Y-, wherein Y represents a single bond, oxygen atom, NR^{24} or $S(O)_w$; and said alkylene being optionally further substituted by OH, halogen, CN, $NR^{37}R^{38}$, C_1-C_3 alkoxy, $CONR^{39}R^{40}$, SO_2R^{41} and $SO_2NR^{42}R^{43}$;

or $\mathbf{R^4}$ and **X** are joined together such that the group $-\mathbf{NR^4X}$ together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{44}; said ring being optionally substituted by C_1-C_6 alkyl or $NR^{45}R^{46}$; said alkyl being optionally further substituted by OH;

either $\mathbf{R}^5$ represents a monocyclic ring system selected from

i) phenoxy,

ii) phenyl,

iii) a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur,

iv) a saturated or partially unsaturated C_3-C_6 hydrocarbyl ring, or

v) a saturated or partially unsaturated 4- to 7-membered heterocyclic ring comprising at least one ring heteroatom selected from oxygen, $S(O)_r$ and NR^{20}, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group,

or $\mathbf{R}^5$ represents a bicyclic ring system in which the two rings are independently selected from the monocyclic ring systems defined in ii), iii), iv) and v) above, wherein the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group selected from oxygen, $S(O)_t$ or C_1-C_6 alkylene optionally comprising one or more internal or terminal heteroatoms selected from oxygen, sulphur and NR^{27} and being optionally substituted by at least one substituent selected from hydroxyl, oxo and C_1-C_6 alkoxy,

the monocyclic or bicyclic ring system being optionally substituted by at least one substituent selected from oxygen, CN, OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, $NR^{47}R^{48}$, NO_2, OSO_2R^{49}, CO_2R^{50}, $C(=NH)NH_2$, $C(O)NR^{51}R^{52}$, $C(S)NR^{53}R^{54}$, $SC(=NH)NH_2$, $NR^{55}C(=NH)NH_2$, $S(O)_vR^{21}$, $SO_2NR^{56}R^{57}$, C_1-C_3 alkoxy substituted by one or more F atoms and C_1-C_3 alkyl substituted by SO_2R^{58} or by one or more F atoms; said C_1-C_6 alkyl being optionally further substituted with at least one substituent selected from cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio and $-C(O)NR^{22}R^{23}$;

or $\mathbf{R}^5$ may also represent H;

$\mathbf{R^{20}}$ represents hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl or C_1-C_6 alkoxycarbonyl;

$\mathbf{R^{21}}$ represents hydrogen, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; said alkyl or cycloalkyl group being optionally further substituted by one or more substituents selected independently from OH, CN, C_1-C_3 alkoxy and $CONR^{59}R^{60}$;

$\mathbf{R^{37}}$ and $\mathbf{R^{38}}$ independently represent H, C_1-C_6 alkyl, formyl or C_2-C_6 alkanoyl;

$\mathbf{R^{47}}$ and $\mathbf{R^{48}}$ independently represent H, C_1-C_6 alkyl, formyl, C_2-C_6 alkanoyl, $S(O)_qR^{61}$ or $SO_2NR^{62}R^{63}$; said alkyl group being optionally further substituted by halogen, CN, C_1-C_4 alkoxy or $CONR^{64}R^{65}$;

$\mathbf{R^{41}}$ and $\mathbf{R^{61}}$ independently represent H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

p is 0, 1 or 2;
q is 0, 1 or 2;
r is 0, 1 or 2;
t is 0, 1 or 2;
w is 0, 1 or 2;
v is 0, 1 or 2;

$\mathbf{R^{22}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$, $\mathbf{R^{26}}$, $\mathbf{R^{27}}$, $\mathbf{R^{31}}$, $\mathbf{R^{32}}$, $\mathbf{R^{39}}$, $\mathbf{R^{40}}$, $\mathbf{R^{42}}$, $\mathbf{R^{43}}$, $\mathbf{R^{44}}$, $\mathbf{R^{45}}$, $\mathbf{R^{46}}$, $\mathbf{R^{49}}$, $\mathbf{R^{50}}$, $\mathbf{R^{51}}$, $\mathbf{R^{52}}$, $\mathbf{R^{53}}$, $\mathbf{R^{54}}$, $\mathbf{R^{55}}$, $\mathbf{R^{56}}$, $\mathbf{R^{57}}$, $\mathbf{R^{58}}$, $\mathbf{R^{59}}$, $\mathbf{R^{60}}$, $\mathbf{R^{62}}$, $\mathbf{R^{63}}$, $\mathbf{R^{64}}$ and $\mathbf{R^{65}}$ each independently represent hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

In the context of the present specification, unless otherwise stated, an alkyl, alkenyl or alkynyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Similarly, an alkylene group may be linear or branched. In the definition of R^{14}, the saturated or unsaturated 3- to 10-membered ring system may have alicyclic or aromatic properties. An unsaturated ring system will be partially or fully unsaturated.

R^1 represents hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In one embodiment of the invention, R^1 represents a C_1-C_4 or C_1-C_2 alkyl group, in particular a methyl group.

W represents a group S, S(O) or $S(O)_2$. In one embodiment of the invention, W represents a group S(O) or $S(O)_2$. In another embodiment, W represents S(O).

Z represents a single bond, $-CH_2-$ or $-NR^{25}-$. In one embodiment of the invention, Z represents a single bond, $-CH_2-$, –NH– or $-NCH_3-$. In another embodiment, Z represents a single bond such that the group W is bonded directly to the group R^{14}.

R^{14} represents H or OH or a group selected from

C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) and

a saturated or unsaturated 3- to 10-membered (e.g. 3-, 4- or 5- to 6-, 7-, 8-, 9- or 10-membered) ring system optionally comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur,

each group being optionally substituted with at least one (e.g. one, two, three or four) substituent independently selected from halogen (e.g. fluorine, chlorine, bromine or

iodine), cyano, CHO, hydroxyl, phenyl, nitro, $-S(O)_pR^{33}$, $-C(O)NR^{31}R^{32}$, C_1-C_4 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl), C_1-C_4 alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy or tert-butoxy), C_2-C_4 alkanoyl (e.g. methylcarbonyl (acetyl), ethylcarbonyl, n-propylcarbonyl or isopropylcarbonyl), C_1-C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl or n-hexoxycarbonyl), C_1-C_3 alkyl substituted by one or more F atoms (e.g. CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CF_3, CF_2CF_3, $CH(CF_3)_2$ and $CH_2CH_2CF_3$), C_1-C_3 alkoxy substituted by one or more F atoms (e.g. OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_2F, OCH_2CF_3, OCF_2CF_3, $OCH(CF_3)_2$ and $OCH_2CH_2CF_3$), $NR^{12}R^{13}$, $C{\equiv}CR^{30}$ and OSO_2R^{34}.

Examples of saturated or unsaturated 3- to 10-membered ring systems that may be used, which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, oxazolyl, 2,3-dihydrobenzofuranyl, tetrahydropyranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include cyclopropyl, isoxazolyl and pyrazolyl.

In an embodiment of the invention, R^{14} represents a group selected from C_1-C_6 alkyl or C_1-C_4 alkyl, and a saturated or unsaturated 3- to 6-membered ring system optionally comprising one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur; each group being optionally substituted by one or two substituents independently selected from halogen, cyano, hydroxyl, nitro, $-S(O)_pR^{33}$, $-C(O)NR^{31}R^{32}$, C_1-C_4 alkyl,

C_1-C_4 alkoxy, C_2-C_4 alkanoyl, C_1-C_3 alkyl substituted by one or more F atoms, C_1-C_3 alkoxy substituted by one or more F atoms, $NR^{12}R^{13}$ and $C{\equiv}CR^{30}$.

In an embodiment of the invention, R^{14} represents a group selected from C_1-C_4 alkyl and a saturated or unsaturated 3- to 6-membered ring system optionally comprising one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur; each group being optionally substituted by one or two substituents independently selected from halogen, cyano, nitro, CF_3 and C≡CH.

In a further embodiment of the invention, R^{14} represents phenyl or a 5- or 6-membered heteroaromatic ring system comprising one to three ring heteroatoms independently selected from nitrogen, oxygen and sulphur; each ring being optionally substituted by one or two substituents independently selected from F, Cl, Br, cyano, nitro, CF_3 and C≡CH.

Examples of a 5- or 6-membered heteroaromatic ring include furanyl, thienyl, pyrrolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyrimidinyl and pyrazinyl. Preferred heteroaromatic rings include thienyl, imidazolyl, pyridinyl, pyrimidinyl and pyrazinyl, especially pyridinyl.

In a further embodiment of the invention, R^{14} represents phenyl optionally substituted by one or two substituents independently selected from F, Cl, Br, cyano, nitro, CF_3 and C≡CH.

In one embodiment, R^6 represents H.

In one embodiment, R^3 represents a phenyl or pyridinyl ring substituted with at least one substituent (e.g. one, two or three substituents) independently selected from halogen (e.g.

fluorine, chlorine, bromine or iodine), cyano, nitro, methyl, trifluoromethyl or methylcarbonyl.

In one embodiment, R^3 represents a phenyl group substituted with one or two substituents independently selected from fluorine, chlorine, cyano, nitro, trifluoromethyl or methylcarbonyl.

In another embodiment, R^3 represents a phenyl group substituted with one or two substituents selected from fluorine, chlorine or trifluoromethyl.

In still another embodiment, R^3 represents a phenyl group substituted with a trifluoromethyl substituent (preferably in the meta position).

R^4 represents hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted with at least one substituent (e.g. one or two substituents) independently selected from fluoro, hydroxyl and C_1-C_6 alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy).

In one embodiment, R^4 represents hydrogen or C_1-C_4 alkyl optionally substituted with one or two substituents independently selected from hydroxyl and C_1-C_4 alkoxy.

In another embodiment, R^4 represents hydrogen.

X represents a single bond, O, NR^{24} or a group -C_1-C_6 alkylene-Y-; said alkylene being optionally further substituted by OH, halogen, CN, $NR^{37}R^{38}$, C_1-C_3 alkoxy, $CONR^{39}R^{40}$, SO_2R^{41} or $SO_2NR^{42}R^{43}$. For the avoidance of doubt, X is orientated such that Y is attached to R^5 in formula (I).

In an embodiment of the invention, Y represents a single bond and the alkylene moiety is a linear or branched C_1-C_6 or C_1-C_4 alkylene, optionally substituted by OH, halogen, CN or C_1-C_3 alkoxy.

In an embodiment of the invention, Y represents a single bond and the alkylene moiety is a linear or branched C_1-C_4 alkylene, optionally substituted by OH, F, CN or OCH_3.

In another embodiment of the invention, X represents methylene.

R^5 represents a monocyclic ring system selected from

i) phenoxy,

ii) phenyl,

iii) a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms) independently selected from nitrogen, oxygen and sulphur,

iv) a saturated or partially unsaturated C_3-C_6 hydrocarbyl ring, or

v) a saturated or partially unsaturated 4- to 7-membered heterocyclic ring comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms) independently selected from oxygen, $S(O)_r$ and NR^{20}, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group,

or R^5 represents a bicyclic ring system in which the two rings are independently selected from the monocyclic ring systems defined in ii), iii), iv) and v) above, wherein the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group selected from oxygen, $S(O)_t$ or C_1-C_6 alkylene optionally comprising one or more (e.g. one or two) internal or terminal heteroatoms selected from oxygen, sulphur and NR^{27} and being optionally substituted by at least one substituent (e.g. one or two substituents) independently selected from hydroxyl, oxo and C_1-C_6 alkoxy (e.g.

methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy),

the monocyclic or bicyclic ring system being optionally substituted (on a ring atom) by at least one substituent (e.g. one, two or three substituents) independently selected from oxygen (e.g. to form an N-oxide), $-S(O)_vR^{21}$, C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), CN, OH, C_1-C_6 alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy), halogen (e.g. fluorine, chlorine, bromine or iodine), $NR^{47}R^{48}$, NO_2, OSO_2R^{49}, CO_2R^{50}, $C(=NH)NH_2$, $C(O)NR^{51}R^{52}$, $C(S)NR^{53}R^{54}$, $SC(=NH)NH_2$, $NR^{55}C(=NH)NH_2$, $SO_2NR^{56}R^{57}$, C_1-C_3 alkyl substituted by SO_2R^{58} or by one or more F atoms (e.g. $CH_2SO_2R^{58}$, $CH_2CH_2SO_2R^{58}$, $CH(SO_2R^{58})CH_3$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CF_3, CF_2CF_3, $CH(CF_3)_2$ and $CH_2CH_2CF_3$) and C_1-C_3 alkoxy substituted by one or more F atoms (e.g. OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_2F, OCH_2CF_3, OCF_2CF_3, $OCH(CF_3)_2$ and $OCH_2CH_2CF_3$); said C_1-C_6 alkyl being optionally further substituted with at least one substituent selected from cyano, hydroxyl, C_1-C_6 alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy), C_1-C_6 alkylthio (e.g. methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, tert-butylthio, n-pentylthio or n-hexylthio) and $-C(O)NR^{22}R^{23}$.

Or R^5 may also represent hydrogen.

Examples of a 5- or 6-membered heteroaromatic ring include furanyl, thienyl, pyrrolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyrimidinyl and pyrazinyl. Preferred heteroaromatic rings include isoxazolyl, pyridinyl, imidazolyl and triazolyl.

Unless otherwise indicated, a "saturated or partially unsaturated C_3-C_6 hydrocarbyl ring" denotes a 3- to 6-membered non-aromatic hydrocarbyl ring optionally incorporating one or more double bonds, examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl. A preferred hydrocarbyl ring is cyclopropyl.

Unless otherwise indicated, a "saturated or partially unsaturated 4- to 7-membered heterocyclic ring" as specified above denotes a 4- to 7-membered non-aromatic heterocyclic ring optionally incorporating one or more double bonds and optionally incorporating a carbonyl group, examples of which include tetrahydrofuranyl, tetramethylene sulfonyl, tetrahydropyranyl, 4-oxo-4H-pyranyl (4H-pyran-4-onyl), pyrrolidinyl, 3-pyrrolinyl, imidazolidinyl, 1,3-dioxolanyl (1,3-dioxacyclopentanyl), piperidinyl, piperazinyl, morpholinyl, perhydroazepinyl (hexamethylene iminyl), pyrrolidonyl and piperidonyl. A preferred saturated or partially unsaturated 4- to 7-membered heterocyclic ring is pyrrolidonyl.

Examples of bicyclic ring systems in which the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group include biphenyl, thienylphenyl, pyrazolylphenyl, phenoxyphenyl, phenylcyclopropyl, naphthyl, indanyl, quinolyl, tetrahydroquinolyl, benzofuranyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, isoquinolyl, chromanyl, indenyl, quinazolyl, quinoxalyl, chromanyl, isocromanyl, 3H-indolyl, 1H-indazolyl, quinuclidyl, tetrahydronaphthyl, dihydrobenzofuranyl, morpholine-4-ylphenyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxinyl and 3,4-dihydro-isochromenyl.

In an embodiment of the invention, R^5 represents a substituted monocyclic ring system as defined above.

In another embodiment of the invention, R^5 represents a substituted bicyclic ring system as defined above.

In another embodiment of the invention, R^5 represents H.

In a further embodiment of the invention, R^5 represents a monocyclic ring system selected from

i) phenoxy,

ii) phenyl,

iii) a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur,

iv) a saturated or partially unsaturated C_3-C_6 hydrocarbyl ring, or

v) a saturated or partially unsaturated 4- to 7-membered heterocyclic ring comprising one or two ring heteroatoms independently selected from oxygen, $S(O)_r$ and NR^{20}, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group,

or R^5 represents a bicyclic ring system in which the two rings are independently selected from the monocyclic ring systems defined in ii), iii), iv) and v) above, wherein the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group selected from oxygen, methylene and $S(O)_t$,

the monocyclic or bicyclic ring system being substituted by one or two substituents independently selected from OH, $-S(O)_vR^{21}$ and C_1-C_4 alkyl.

In a still further embodiment of the invention, R^5 represents a monocyclic ring system selected from phenyl or a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms independently selected from nitrogen and oxygen, the monocyclic ring system being substituted by one or two substituents independently selected from OH, $-S(O)_vR^{21}$ and C_1-C_4 alkyl.

In one embodiment p is 2.

R^{20} represents hydrogen, C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6 alkylcarbonyl (e.g. methylcarbonyl (acetyl), ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, isobutylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), or C_1-C_6 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl or n-hexoxycarbonyl).

In a further embodiment, R^{20} represents hydrogen, methyl, ethyl, methylcarbonyl (acetyl), ethylcarbonyl, methoxycarbonyl or ethoxycarbonyl.

In one embodiment, v is 2.

R^{21} represents hydrogen, C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) or C_3-C_8 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl); said alkyl or cycloalkyl group being optionally further substituted by one or more substituents selected independently from OH, CN, C_1-C_3 alkoxy and $CONR^{59}R^{60}$.

In an embodiment according to the invention, R^{21} represents C_1-C_4 alkyl or C_3-C_6 cycloalkyl.

In another embodiment, R^{21} represents C_1-C_3 alkyl (particularly methyl, ethyl or isopropyl) or cyclopropyl.

R^{41} represents hydrogen, C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) or C_3-C_8 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

In an embodiment according to the invention, R^{41} represents C_1-C_4 alkyl or C_3-C_6 cycloalkyl.

In another embodiment, R^{41} represents C_1-C_3 alkyl (particularly methyl, ethyl or isopropyl) or cyclopropyl.

R^{10}, R^{11}, R^{12} and R^{13} each independently represent hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^{10}, R^{11}, R^{12} and R^{13} each independently represent hydrogen or methyl.

R^{15}, R^{16}, R^{17}, R^{18} and R^{19} each independently represent hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} each independently represent hydrogen or methyl.

R^{22} and R^{23} each independently represent hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^{22} and R^{23} each independently represent hydrogen.

R^{24} represents hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^{24} represents hydrogen.

R^{27} represents hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^{27} represents hydrogen.

In an embodiment of the invention,

R^1 represents methyl;

W represents S(O);

Z represents a single bond;

R^{14} represents phenyl optionally substituted by one or two substituents independently selected from cyano, F, Cl, Br, CF_3, NO_2 and -C≡CH;

R^6 represents H;

R^3 represents a phenyl group substituted with a trifluoromethyl substituent;

R^4 represents hydrogen;

X represents methylene; and

R^5 represents phenyl or pyridinyl substituted by $-S(O)_vR^{21}$ wherein v represents the integer 2.

In an embodiment of the invention,

R^1 represents methyl;

W represents S(O);

Z represents a single bond;

R^{14} represents phenyl optionally substituted by one or two substituents independently selected from cyano, F, Cl, Br, CF_3, NO_2 and -C≡CH;

R^6 represents H;

R^3 represents a phenyl group substituted with a trifluoromethyl substituent;

R^4 represents hydrogen;

X represents a linear or branched C_1-C_4 alkylene optionally substituted by OH, F, CN or OCH_3; and

$\mathbf{R^5}$ represents H.

Examples of compounds of the invention include:

N-Cyclopropyl-5-[(4-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

2-Oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Bromophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(2,4-Dimethoxybenzyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-cyclopropyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-{[5-(Cyclopropylsulfonyl)pyridin-2-yl]methyl}-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-(methylsulfinyl)-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Cyclopropyl-5-[(3-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Cyclopropyl-5-[(2-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[(2*S*)-2-hydroxypropyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(2-Cyanoethyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-cyclopropyl-1-(3,5-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-dichlorophenyl)-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-dichlorophenyl)-*N*,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-6-methyl-*N*-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-[(3-methylisoxazol-5-yl)methyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Cyclopropyl-5-[(4-hydroxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethy)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[3-(1*H*-imidazol-1-yl)propyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-*N*-[3-(1*H*-1,2,3-triazol-1-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[(1-hydroxycyclopropyl)methyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

1-(3-Cyanophenyl)-5-[(4-cyanophenyl)sulfinyl]-6-methyl-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-methoxyethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxy-2-methylpropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Chlorophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-[(4-methylphenyl)sulfinyl]-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-[(4-nitrophenyl)sulfinyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-{[4-(trifluoromethyl)phenyl]sulfinyl}-1,2-dihydropyridine-3-carboxamide;

5-{[4-(Acetylamino)phenyl]sulfinyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Ethylphenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Fluorophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-1-(3-methylphenyl)-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-ethyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Chlorophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Ethyl-5-[(4-fluorophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Fluorophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Bromophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxyethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(cyclopropylmethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Methyl-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-(Cyanomethyl)-5-[(4-cyanophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxypropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-(2-morpholin-4-ylethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxy-1,1-dimethylethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[(2*R*)-2-hydroxypropyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-methoxypropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-(methylsulfonyl)-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

2-Oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-5-(phenylsulfonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-{[4-(Acetylamino)phenyl]sulfonyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Ethylphenyl)sulfonyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfonyl]-*N*-(2-hydroxy-1,1-dimethylethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-[(3-Cyclopropylisoxazol-5-yl)methyl]-6-methyl-5-(methylsulfonyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(6-Cyanopyridin-3-yl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-({4-[(trimethylsilyl)ethynyl]phenyl}sulfinyl)-1,2-dihydropyridine-3-carboxamide;

5-[(4-Ethynylphenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-{[4-(phenylethynyl)phenyl]sulfinyl}-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-[(4-prop-1-yn-1-ylphenyl)sulfinyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Cyanopyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-({2-Methyl-5-(methylcarbamoyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}sulfinyl)nicotinamide;

5-[(5-Chloropyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Bromopyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Cyanopyridin-2-yl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Bromopyrimidin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(6-Bromopyridazin-3-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(6-Cyanopyridin-3-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Cyano-2-thienyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-(1*H*-Imidazol-2-ylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-[(methylamino)sulfonyl]-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-(Anilinosulfonyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-{[(2-morpholin-4-ylethyl)amino]sulfonyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-{[(2-Cyanoethyl)(methyl)amino]sulfonyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-{[(6-morpholin-4-ylpyridin-3-yl)amino]sulfonyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-(morpholin-4-ylsulfonyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

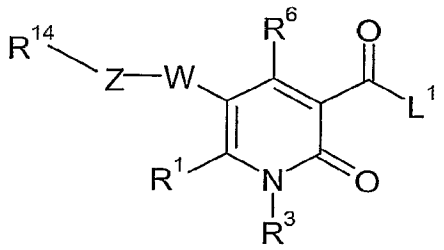
6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-[(pyridin-3-ylamino)sulfonyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

2-Methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-sulfonic acid;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylthio)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylsulfonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
6-Methyl-5-(methylsulfinyl)-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
6-Methyl-5-(methylsulfonyl)-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
5-(Benzylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
5-(Ethylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
Methyl 3-({2-methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}sulfinyl)propanoate;
5-(Cyclohexylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
5-(Cyclopropylsulfonyl)-N-[4-(cyclopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
and pharmaceutically acceptable salts of any one thereof.

The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises,

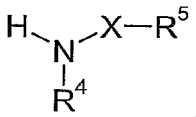
(a) reacting a compound of formula (II)



(II)

wherein L^1 represents a leaving group (such as halogen or hydroxyl) and R^1, R^3, R^6, R^{14}, W and Z are as defined in formula (I),

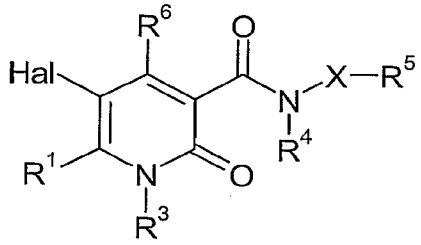
with a compound of formula



(III)

wherein X, R^4 and R^5 are as defined in formula (I); or

(b) when W represents –S– and Z represents a single bond or $–CH_2–$, reacting a compound of formula (IV)



(IV)

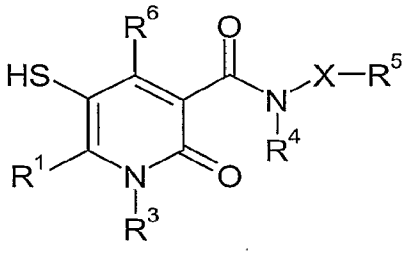
wherein Hal represents a halogen atom and X, R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with a nucleophile R^{14}–Z–S–M wherein R^{14} and Z are as defined in formula (I) and M represents an organo-tin or organo boronic acid group; or

(c) when W represents –S– and Z represents a single bond or $–CH_2–$, reacting a compound of formula (IV) wherein Hal represents a halogen atom and X, R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with a thiol $R^{14}–Z–S–H$ wherein R^{14} and Z are as defined in formula (I) in the presence of a copper (I) salt; or

(d) when W represents –S– and Z represents a single bond or $–CH_2–$, reacting a compound of formula (V)

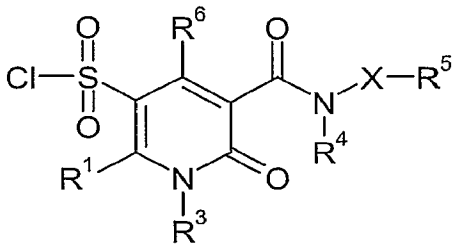


(V)

wherein X, R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with an electrophile $R^{14}–Z–L^2$ wherein L^2 represents a leaving group such as halogen and R^{14} and Z are as defined in formula (I); or

(e) when W represents $–SO_2–$ and Z represents $–NR^{25}–$, reacting a compound of formula (VI)



(VI)

wherein X, R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with an amine R^{14}–NHR^{25} wherein R^{14} and R^{25} are as defined in formula (I); or

(f) when W represents a sulfinyl (–S(O) –) or a sulfonyl (–$S(O)_2$–) group, oxidising the corresponding compound wherein W represents a thio (–S –) group;

and optionally after (a), (b), (c), (d), (e) or (f) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

In process (a), the reaction may conveniently be carried out in an organic solvent such as dichloromethane or N-methylpyrrolidinone at a temperature, for example, in the range from 0 °C to the boiling point of the solvent. If necessary or desired, a base and/or a coupling reagent such as HATU (O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate), HOAT (1-Hydroxy-7-azabenzotriazole), HOBT (1-Hydroxybenzotriazole hydrate) or DIEA (N,N-Diisopropylethylamine) may be added.

In process (b), the reaction may conveniently be carried out in an organic solvent such as DMF, NMP or toluene or a mixture thereof at elevated temperature (i.e. above ambient temperature, 20°C), for example, in the range from 50 °C to 150 °C and in the presence of a suitable transition metal catalyst such as bis(tri-*t*-butylphosphine)palladium. If necessary or desired, a base such as potassium carbonate may be added.

In process (c), the reaction may conveniently be carried out in an organic solvent such as acetonitrile at elevated temperature (i.e. above ambient temperature, 20°C), for example, in the range from 50 °C to the boiling point, and in the presence of a salt such as copper (I) iodide and an amine such as (±)-trans-cyclohex-1,2-diamine.

In process (d), the reaction may conveniently be carried out in an organic solvent such as acetonitrile or dioxane at elevated temperature (i.e. above ambient temperature, 20°C), for example, in the range from 40 °C to the boiling point, and in the presence of a salt such as copper (I) iodide and an amine such as (±)-trans-cyclohex-1,2-diamine. Alternatively, the reaction may be carried out in the presence of a base such as caesium carbonate.

In process (e), the reaction may conveniently be carried out in an organic solvent such as tetrahydrofuran, optionally in the presence of a base.

In process (f), the oxidation may conveniently be carried out using hydrogen peroxide or sodium periodate. Other suitable oxidants will be readily apparent to the man skilled in the art.

Specific processes for the preparation of compounds of Formula (I) are disclosed within the Examples section of the present specification. Such processes form an aspect of the present invention.

The necessary starting materials are either commercially available, are known in the literature or may be prepared using known techniques. Specific processes for the preparation of certain key starting materials are disclosed within the Examples section of the present specification and such processes form an aspect of the present invention.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups may need to be

protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the addition and/or removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as modulators of serine proteases such as proteinase 3 and pancreatic elastase and, especially, human neutrophil elastase, and may therefore be beneficial in the treatment or prophylaxis of inflammatory diseases and conditions.

Examples of such conditions include: adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD) and ischaemic-reperfusion injury. The compounds of this invention may also be useful in the modulation of endogenous and/or exogenous biological irritants which cause and/or propagate atherosclerosis, diabetes, myocardial infarction; hepatic disorders including but not limited to cirrhosis, systemic lupus erythematous, inflammatory disease of lymphoid origin, including but not limited to T lymphocytes, B lymphocytes,

thymocytes; autoimmune diseases, bone marrow; inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout); inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis, pancreatitis and gastritis); inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); age related illness such as dementia, inflammatory diseases of cardiovascular origins; granulomatous diseases; renal diseases including but not limited to nephritis and polyarteritis; cancer; pulmonary hypertension, ingested poisons, skin contacts, stings, bites; asthma; rhinitis; HIV disease progression; for minimising the effects of organ rejection in organ transplantation including but not limited to human organs; and replacement therapy of proteinase inhibitors.

Thus, the present invention provides a compound of formula (I) or a pharmaceutically-acceptable salt thereof as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or

those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The invention also provides a method of treating, or reducing the risk of, a disease or condition in which inhibition of neutrophil elastase activity is beneficial which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

The invention still further provides a method of treating, or reducing the risk of, an inflammatory disease or condition which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

In particular, the compounds of this invention may be used in the treatment of adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma, rhinitis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, cancer, atherosclerosis and gastric mucosal injury.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of the invention may be in the range from 0.05 mg/kg to 100 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 μm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_8-C_{20} fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for

tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The present invention will now be further explained by reference to the following illustrative examples.

General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian *Inova* 400 MHz or a Varian *Mercury*-VX 300 MHz instrument. The central peaks of chloroform-*d* (δ_H 7.27 ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm), acetonitrile-d_3 (δ_H 1.95 ppm) or methanol-d_4 (δ_H 3.31 ppm) were used as internal references. Column chromatography was carried out using silica gel (0.040-0.063 mm, Merck). Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

The following method was used for LC/MS analysis:
Instrument Agilent 1100; Column Waters Symmetry 2.1 x 30 mm; Mass APCI; Flow rate 0.7 ml/min; Wavelength 254 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA ; Gradient 15-95%/B 8 min, 95% B 1 min.

Analytical chromatography was run on a Symmetry C_{18}-column, 2.1 x 30 mm with 3.5 µm particle size, with acetonitrile/water/0.1% trifluoroacetic acid as mobile phase in a gradient from 5% to 95% acetonitrile over 8 minutes at a flow of 0.7 ml/min.

The abbreviations or terms used in the examples have the following meanings:

HATU:	O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
HOAT:	1-Hydroxy-7-azabenzotriazole
NMP:	1-N-Methyl-2-pyrrolidinone
THF:	Tetrahydrofuran
TFA:	Trifluoroacetic acid
DMF:	N,N-Dimethylformamide
DCM:	Dichloromethane
DIPEA:	N,N-Diisopropylethylamine
EtOAc:	Ethyl acetate
MeOH:	Methanol
MeCN	Acetonitrile
EtOH:	Ethanol
NaS_2O_4:	Sodium hydrosulphite
DMSO:	Dimethyl sulphoxide
SM:	Starting material
Ex:	Example
Aq:	Aqueous
HOAc:	Acetic acid
RT:	Room temperature
DABCO:	1,4-Diazabicyclo[2.2.2]octane.

Example 1

N-Cyclopropyl-5-[(4-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of *N*-cyclopropyl-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (SM3, 25 mg, 0.054 mmol), tributyl-[(4-methoxyphenyl)thio]stannane (28 mg, 0.065 mmol), palladium - tri-*tert*-butylphosphine (1:2) (2.6 mg, 0.005 mmol) and NMP (1 ml) under argon was heated in a microwave to 150 °C for 10 min. After filtration, the crude compound was purified on an Xterra C8 column using a gradient of acetonitrile/water. The residue obtained on evaporation was dissolved in acetic acid (3 ml) and hydrogen peroxide (35% in water, 100 µl) was added. The mixture was stirred for 3h at room temperature. Then diluted with water (5 ml) and extracted with ethyl acetate (3 x 5 ml). The organic phase was dried (MgSO4), filtered and evaporated. The residue was purified on an Xterra C8 column using a gradient of acetonitrile/water. Freeze drying of the mixture afforded the title compound (10 mg, 38 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.80 (d, J = 5.5 Hz, 1H), 7.82 (t, J = 7.8 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 2.9 Hz, 2H), 7.58 (d, J = 2.8 Hz, 2H), 7.49 - 7.36 (m, 2H), 7.07 (d, J = 2.9 Hz, 2H), 7.04 (d, J = 3.1 Hz, 2H), 3.88 (s, 3H), 2.90 (m, 1H), 2.35 (d, J = 5.1 Hz, 3H), 0.77 (dd, J = 7.2, 1.0 Hz, 2H), 0.52 (dd, J = 6.0, 1.2 Hz, 2H);

APCI-MS m/z: 491.2 [MH^+]

Examples 2 to 13

The following compounds were synthesised using an analogous method to that described for Example 1.

Ex.	Compound	^{1}H NMR	m/z	SM
2	2-Oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.26 (t, J = 5.9 Hz, 1H), 8.78 (d, J = 2.8 Hz, 1H), 8.27 (d, J = 2.8 Hz, 1H), 8.11 (s, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.87 - 7.72 (m, 3H), 7.67 - 7.53 (m, 3H), 3.33 - 3.09 (m, 6H), 2.16 (t, J = 8.1 Hz, 2H), 1.86 (quintet, J = 7.6 Hz, 2H), 1.62 (quintet, J = 6.9 Hz, 2H)	532.1	SM2

3	5-[(4-Bromophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.65 (t, *J* = 6.0 Hz, 1H), 8.38 (s, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 7.88 - 7.77 (m, 6H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 4.60 - 4.46 (m, 2H), 3.16 (s, 3H), 2.32 (s, 3H)	667.0, 669.0	SM1
4	5-[(2,4-Dimethoxybenzyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.74 (t, *J* = 5.9 Hz, 1H), 8.73 (d, *J* = 16.0 Hz, 1H), 7.95 - 7.78 (m, 4H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.56 (dd, *J* = 8.2, 2.1 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 9.1 Hz, 1H), 6.59 - 6.48 (m, 2H), 4.61 (m, 2H), 4.25 (dd, *J* = 11.9, 9.8 Hz, 1H), 4.00 (dd, *J* = 12.0, 3.1 Hz, 1H), 3.77 - 3.68 (m, 6H), 3.18 (s, 3H), 1.54 (d, *J* = 6.2 Hz, 3H)	663.0	SM1
5	5-[(4-Cyanophenyl)sulfinyl]-*N*-cyclopropyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.05 (s, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 2H), 8.01 - 7.74 (m, 6H), 2.76 (m, 1H), 2.34 (s, 3H), 0.67 (d, *J* = 7.5 Hz, 2H), 0.45 (q, *J* = 3.7 Hz, 2H).	486.1	SM3
6	*N*-{[5-(Cyclopropylsulfonyl)-pyridin-2-yl]methyl}-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.93 (t, *J* = 5.7 Hz, 1H), 8.94 (dd, *J* = 2.4, 0.7 Hz, 1H), 8.83 (d, *J* = 2.8 Hz, 1H), 8.29 (d, *J* = 2.8 Hz, 1H), 8.22 (dd, *J* = 8.3, 2.4 Hz, 1H), 8.13 (s, 1H), 8.00 - 7.51 (m, 9H), 4.69 (d, *J* = 5.9 Hz, 2H), 2.94 (m, 1H), 1.19 - 1.00 (m, 4H)	602.1	SM4

7	6-Methyl-5-(methylsulfinyl)-*N*-{[5-(methylsulfonyl)-pyridin-2-yl]methyl}-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.96 (t, *J* = 5.7 Hz, 1H), 8.99 (d, *J* = 2.2 Hz, 1H), 8.79 (d, *J* = 1.9 Hz, 1H), 8.27 (dd, *J* = 8.2, 2.4 Hz, 1H), 8.03 - 7.72 (m, 4H), 7.58 (d, *J* = 8.2 Hz, 1H), 4.74 (d, *J* = 5.1 Hz, 2H), 3.29 (s, 3H), 2.78 (d, *J* = 3.3 Hz, 3H), 2.08 (d, *J* = 2.7 Hz, 3H)	528.1	SM5
8	*N*-Cyclopropyl-5-[(3-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.07 (s, 1H), 8.77 (d, *J* = 9.1 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.77 (q, *J* = 7.8 Hz, 1H), 7.49 - 7.39 (m, 3H), 7.30 (dd, *J* = 4.4, 1.9 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 3.93 (s, 3H), 2.90 - 2.87 (m, 1H), 2.39 (d, *J* = 7.2 Hz, 3H), 0.77 (d, *J* = 7.2 Hz, 2H), 0.51 (d, *J* = 3.5 Hz, 2H)	491.1	SM3
9	*N*-Cyclopropyl-5-[(2-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.16 (s, 1H), 8.70 (d, *J* = 6.1 Hz, 1H), 8.07 (dt, *J* = 7.7, 1.9 Hz, 1H), 7.83 (t, *J* = 7.4 Hz, 1H), 7.76 (m, 1H), 7.55 - 7.48 (m, 2H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.31 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.93 - 6.90 (m, 1H), 3.83 (d, *J* = 3.7 Hz, 3H), 2.91 - 2.84 (m, 1H), 2.41 (d, *J* = 2.2 Hz, 3H), 0.79 - 0.72 (m, 2H), 0.55 - 0.46 (m, 2H)	491.2	SM3

10	5-[(4-Cyanophenyl)sulfinyl]-*N*-[(2*S*)-2-hydroxypropyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.35 (s, 1H), 8.66 (d, *J* = 12.5 Hz, 1H), 7.88 - 7.81 (m, 3H), 7.81 - 7.77 (m, 3H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 8.7 Hz, 1H), 3.95 (m, 1H), 3.51 - 3.47 (m, 1H), 3.34 - 3.28 (m, 1H), 2.42 (d, *J* = 7.3 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H)	504.1	SM6
11	5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	8.41 (s, 2H), 8.31 (d, *J* = 2.6 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 2H), 8.00 (d, *J* = 5.6 Hz, 1H), 7.97 - 7.72 (m, 6H), 2.34 (s, 3H)	446.0	SM7
12	5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.63 (t, *J* = 6.0 Hz, 1H), 8.32 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.97 - 7.77 (m, 7H), 7.49 (d, *J* = 8.2 Hz, 2H), 4.53 (d, *J* = 6.0 Hz, 2H), 3.15 (s, 3H), 2.36 (s, 3H)	614.0	SM1
13	5-[(2-Cyanoethyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.75 (t, *J* = 6.1 Hz, 1H), 8.70 (d, *J* = 1.1 Hz, 1H), 7.99 - 7.76 (m, 5H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 4.67 - 4.51 (m, 2H), 3.41 - 3.19 (m, 2H), 3.18 (s, 3H), 3.02 - 2.77 (m, 2H), 2.09 (d, *J* = 2.2 Hz, 3H)	566.4	SM1

Example 14

5-[(4-Cyanophenyl)sulfinyl]-*N*-cyclopropyl-1-(3,5-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

To a mixture of *N*-cyclopropyl-1-(3,5-difluorophenyl)-5-iodo-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (SM8, 25 mg, 0.058 mmol), copper(I) iodide (1.9 mg, 0.01

mmol) and (±)-*trans*-cyclohexane-1,2-diamine (1.14 mg, 0.01 mmol) in acetonitrile (1.5 ml), 4-mercaptobenzonitrile (10 mg, 0.075 mmol) was added and the mixture was heated in a microwave reactor to 90 °C for 15 min. The residue obtained on evaporation was then diluted with water (15 ml) and extracted with ethyl acetate. The organic phase was dried (MgSO4), filtered and evaporated. To the residue dissolved in acetic acid (1 ml) was added hydrogen peroxide (35% in water, 0.10 ml). The mixture was stirred overnight at room temperature. The compound was then purified on an Xterra C8 column using a gradient of acetonitrile/water. Freeze drying of the collected fractions afforded the title compound (3 mg, 7%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (t, J = 3.5 Hz, 1H), 8.64 (s, 1H), 7.86 (dd, J = 6.8, 1.8 Hz, 2H), 7.77 (dd, J = 6.7, 1.7 Hz, 2H), 7.10 - 7.03 (m, 1H), 6.83 - 6.78 (m, 2H), 2.92 - 2.86 (m, 1H), 2.48 (s, 3H), 0.80 - 0.76 (m, 2H), 0.54 - 0.49 (m, 2H);
APCI-MS m/z: 454.0 [MH^+].

Examples 15 to 43

The following compounds were synthesised using an analogous method to that described for Example 14.

Ex.	Compound	^{1}H NMR	m/z	SM
15	5-[(4-Cyanophenyl)sulfinyl]-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	10.05 (t, J = 5.3 Hz, 1H), 9.03 (d, J = 1.7 Hz, 1H), 8.54 (d, J = 2.7 Hz, 1H), 8.13 (dd, J = 5.9, 2.5 Hz, 2H), 7.85 (d, J = 11.0 Hz, 5H), 7.75 (t, J = 7.9 Hz, 1H), 7.70 (s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 4.83 (d, J = 5.5 Hz, 2H), 3.13 (q, J = 7.4 Hz, 2H), 1.32 - 1.25 (m, 3H)	615.5	SM9

16	5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide	9.85 (t, 1H), 9.03 (s, 1H), 8.65 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.08 (t, J = 8.6 Hz, 1H), 6.83 (t, J = 6.9 Hz, 2H), 4.83 (d, 2H), 3.14 (q, J = 7.4 Hz, 2H), 2.50 (s, 3H), 1.32 - 1.26 (m, 3H)	597.2	SM10
17	5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-dichlorophenyl)-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide	9.79 (t, 1H), 8.92 (d, J = 1.7 Hz, 1H), 8.32 (s, 1H), 8.09 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 7.4 Hz, 2H), 7.54 (d, J = 8.3 Hz, 1H), 4.68 (d, J = 4.5 Hz, 3H), 3.37 - 3.32 (m, 2H), 2.43 (s, 3H), 1.10 (t, J = 7.3 Hz, 3H)	629.2	SM11
18	5-[(4-Cyanophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.06 (d, J = 4.8 Hz, 1H), 8.86 (d, J = 2.8 Hz, 1H), 8.23 (d, J = 2.6 Hz, 1H), 8.10 (quintet, J = 2.1 Hz, 3H), 7.97 - 7.92 (m, 4H), 7.84 (d, J = 7.9 Hz, 1H), 2.76 (d, J = 4.8 Hz, 3H)	446.2	SM12
19	5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-dichlorophenyl)-*N*,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide	8.95 (d, J = 4.7 Hz, 1H), 8.28 (s, 1H), 8.09 (d, J = 8.3 Hz, 2H), 7.90 - 7.86 (m, 3H), 7.72 (dd, J = 4.1, 1.6 Hz, 2H), 2.74 (d, J = 4.8 Hz, 3H), 2.41 (s, 3H)		SM13
20	5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide	9.18 (t, J = 6.0 Hz, 1H), 8.89 (s, 1H), 8.29 (s, 1H), 8.10 (dt, J = 8.5, 1.8 Hz, 2H), 7.88 (dt, J = 8.5, 1.7 Hz, 2H), 7.57 - 7.49 (m, 1H), 7.40 - 7.36 (m, 3H), 3.55 (q, J = 6.4 Hz, 2H), 2.84 (t, J = 6.6 Hz, 2H), 2.42 (s, 3H)	492.1	SM14

21	5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-6-methyl-*N*-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-pyridine-3-carboxamide		527.1	SM15
22	5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*,6-dimethyl-2-oxo-1,2-dihydro-pyridine-3-carboxamide	9.01 (d, J = 4.0 Hz, 1H), 8.64 (s, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H), 7.07 (tt, J = 8.6, 2.2 Hz, 1H), 6.82 - 6.79 (m, 2H), 2.91 (d, J = 5.0 Hz, 3H), 2.49 (s, 3H)	428.2	SM16
23	5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-[(3-methylisoxazol-5-yl)methyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.55 (t, J = 5.3 Hz, 1H), 8.10 (d, J = 7.5 Hz, 1H), 8.01 (d, J = 7.8 Hz, 2H), 7.87 (m, 6H), 6.11 (s, 1H), 4.53 (m, Hz, 2H), 2.36 (d, J = 2.3 Hz, 3H), 2.16 (d, J = 9.7 Hz, 3H)	541.0	SM17
24	*N*-Cyclopropyl-5-[(4-hydroxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethy)phenyl]-1,2-dihydropyridine-3-carboxamide	9.39 (s, 1H), 8.87 (d, J = 7.3 Hz, 1H), 7.87 - 7.74 (m, 2H), 7.59 - 7.54 (m, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.7 Hz, 1H), 7.11 - 7.07 (m, 1H), 2.88 (dq, J = 7.2, 3.7 Hz, 2H), 2.42 (d, J = 4.2 Hz, 2H), 0.81 (dt, J = 8.5, 1.2 Hz, 2H), 0.54 (dd, J = 10.0, 4.1 Hz, 2H)	477.1	SM3
25	5-[(4-Cyanophenyl)sulfinyl]-*N*-[3-(1*H*-imidazol-1-yl)propyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.20 (s, 1H), 9.07 (s, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 8.02 - 7.73 (m, 7H), 7.65 (s, 1H), 4.15 (t, J = 7.0 Hz, 2H), 3.24 (q, J = 6.4 Hz, 2H), 2.37 (s, 3H), 1.99 (quintet, J = 6.9 Hz, 2H)	554.2	SM18

26	5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-*N*-[3-(1*H*-1,2,3-triazol-1-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.20 (s, 1H), 8.31 (d, J = 2.5 Hz, 1H), 8.13 - 8.08 (m, 3H), 8.03 - 7.78 (m, 6H), 7.68 (d, J = 0.9 Hz, 1H), 4.34 (t, J = 7.0 Hz, 2H), 3.28 - 3.16 (m, 2H), 2.36 (s, 3H), 1.99 (quintet, J = 6.9 Hz, 2H)	555.4	SM19
27	5-[(4-Cyanophenyl)sulfinyl]-*N*-[(1-hydroxycyclopropyl)-methyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.35 (t, J = 5.1 Hz, 1H), 8.32 (d, J = 1.5 Hz, 1H), 8.13 - 7.78 (m, 9H), 3.31 (m, 2H), 2.35 (s, 3H), 0.57 - 0.38 (m, 4H)	516.2	SM20
28	1-(3-Cyanophenyl)-5-[(4-cyanophenyl)sulfinyl]-6-methyl-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxamide	δ 9.80 (t, J = 5.9 Hz, 1H), 8.96 (d, J = 1.8 Hz, 1H), 8.34 (d, J = 5.8 Hz, 1H), 8.24 (dd, J = 8.2, 2.2 Hz, 1H), 8.13 - 8.04 (m, 4H), 7.92 - 7.81 (m, 4H), 7.53 (d, J = 8.3 Hz, 1H), 4.57 (m, 2H), 3.28 (s, 3H), 3.28 (s, 3H)	572.2	SM5
29	5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-methoxyethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.21 (s, 1H), 8.32 (d, J = 1.7 Hz, 1H), 8.24 - 7.78 (m, 8H), 3.46 - 3.30 (m, 4H), 3.19 (s, 3H), 2.35 (s, 3H)	504.1	SM21
30	5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxy-2-methylpropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.27 (t, J = 5.4 Hz, 1H), 8.33 (d, J = 1.5 Hz, 1H), 8.10 (d, J = 8.6 Hz, 2H), 8.02 (s, 1H), 7.98 - 7.78 (m, 6H), 3.21 - 3.14 (m, 2H), 2.34 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H)	518.5	SM22

31	5-[(4-Chlorophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	δ 9.66 (t, *J* = 6.0 Hz, 1H), 8.39 (d, *J* = 0.9 Hz, 1H), 8.01 (d, *J* = 5.7 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.89 - 7.66 (m, 8H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.54 (dd, *J* = 8.4, 5.6 Hz, 2H), 3.16 (s, 3H), 2.32 (s, 3H)	623.3, 625.3	SM1
32	6-Methyl-5-[(4-methylphenyl)sulfinyl]-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.67 (t, *J* = 6.1 Hz, 1H), 8.43 (d, *J* = 2.3 Hz, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 6.9 Hz, 1H), 7.89 - 7.77 (m, 4H), 7.59 (dd, *J* = 6.5, 1.7 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 4.54 (m, 2H), 3.15 (s, 3H), 2.37 (s, 3H), 2.31 (d, *J* = 0.5 Hz, 3H)	603.1	SM1
33	6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-[(4-nitrophenyl)sulfinyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.63 (t, *J* = 6.1 Hz, 1H), 8.42 (dd, *J* = 9.0, 0.9 Hz, 2H), 8.35 (d, *J* = 1.1 Hz, 1H), 8.05 - 7.77 (m, 8H), 7.49 (d, *J* = 8.4 Hz, 2H), 4.52 (m, 2H), 3.15 (s, 3H), 2.38 (s, 3H)	634.0	SM1
34	6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-5-{[4-(trifluoromethyl)phenyl]sulfinyl}-1,2-dihydropyridine-3-carboxamide	9.64 (t, *J* = 6.1 Hz, 1H), 8.37 (s, 1H), 8.04 - 7.77 (m, 10H), 7.49 (d, *J* = 8.2 Hz, 2H), 4.53 (m, 2H), 3.15 (s, 3H), 2.37 (s, 3H)	657.0	SM1

35	5-{[4-(Acetylamino)phenyl]-sulfinyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	10.26 (s, 1H), 9.68 (t, *J* = 6.0 Hz, 1H), 8.46 (d, *J* = 2.9 Hz, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 7.0 Hz, 1H), 7.88 - 7.75 (m, 6H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 4.54 (m, 2H), 3.15 (s, 3H), 2.28 (d, *J* = 1.7 Hz, 3H), 2.07 (s, 3H)	646.1	SM1
36	5-[(4-Ethylphenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.68 (t, *J* = 6.1 Hz, 1H), 8.45 (d, *J* = 1.7 Hz, 1H), 8.02 (s, 1H), 7.93 (d, *J* = 6.5 Hz, 1H), 7.89 - 7.76 (m, 4H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.53 - 7.41 (m, 4H), 4.54 (m, 2H), 3.15 (s, 3H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.31 (d, *J* = 0.7 Hz, 3H), 1.19 (t, *J* = 7.6 Hz, 3H)	617.1	SM1
37	5-[(4-Fluorophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.67 (t, *J* = 6.0 Hz, 1H), 8.42 (d, *J* = 1.4 Hz, 1H), 8.01 (d, *J* = 6.9 Hz, 1H), 7.93 (d, *J* = 7.1 Hz, 1H), 7.89 - 7.73 (m, 6H), 7.54 - 7.43 (m, 4H), 4.23 (m, 2H), 3.16 (s, 3H), 2.32 (s, 3H)	607.3	SM1
38	5-[(4-Cyanophenyl)sulfinyl]-6-methyl-1-(3-methylphenyl)-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxamide	9.90 (t, *J* = 5.6 Hz, 1H), 8.96 (d, *J* = 1.7 Hz, 1H), 8.31 (s, 1H), 8.24 (dd, *J* = 8.2, 2.3 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.90 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.57 - 7.45 (m, 2H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.28 - 7.21 (m, 2H), 4.67 (d, *J* = 4.4 Hz, 2H), 3.28 (s, 3H), 2.38 (s, 3H), 2.38 (s, 3H)	561.1	SM5

39	5-[(4-Cyanophenyl)sulfinyl]-*N*-ethyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.08 (t, J = 5.6 Hz, 1H), 8.31 (d, J = 1.5 Hz, 1H), 8.10 (d, J = 7.8 Hz, 2H), 8.04 - 7.76 (m, 6H), 3.23 (ddd, J = 20.1, 7.3, 2.1 Hz, 2H), 2.35 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H)	474.0	SM23
40	5-[(4-Chlorophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.01 (d, J = 4.8 Hz, 1H), 8.36 (d, J = 2.0 Hz, 1H), 8.02 - 7.65 (m, 8H), 2.74 (d, J = 4.8 Hz, 3H), 2.32 (s, 3H)	469.3, 471.2	SM24
41	*N*-Ethyl-5-[(4-fluorophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.12 (t, J = 5.4 Hz, 1H), 8.40 (d, J = 1.9 Hz, 1H), 8.04 - 7.72 (m, 6H), 7.53 - 7.43 (m, 2H), 3.24 (m, 2H), 2.30 (d, J = 0.7 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H)	467.3	SM23
42	5-[(4-Fluorophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.02 (d, J = 4.4 Hz, 1H), 8.39 (d, J = 3.0 Hz, 1H), 8.03 - 7.73 (m, 6H), 7.52 - 7.43 (m, 2H), 2.75 (d, J = 4.4 Hz, 3H), 2.31 (s, 3H)	453.2	SM24
43	5-[(4-Bromophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.01 (q, J = 4.6 Hz, 1H), 8.36 (d, J = 2.5 Hz, 1H), 7.99 (d, J = 4.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.88 - 7.76 (m, 4H), 7.65 (d, J = 8.5 Hz, 2H), 2.74 (d, J = 4.2 Hz, 3H), 2.31 (s, 3H)	515.2, 513.2	SM24

Example 44

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxyethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To a mixture of 5-[(4-cyanophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid (SM25, 25 mg, 0.056

mmol) and HATU (21 mg, 0.056 mmol) in NMP (1 ml) was added ethanol amine (7 mg, 0.12 mmol) and DIPEA (0.12 mmol). The reaction was heated in a microwave reactor to 50 °C for 10 min. The crude compound was then purified on an Xterra C8 column using a gradient of acetonitrile/water. Freeze drying afforded the title compound (1 mg, 4%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H), 8.42 (s, 1H), 8.25 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.9 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 5.09 (t, J = 5.4 Hz, 1H), 4.30 - 4.24 (m, 2H), 3.76 (d, J = 5.5 Hz, 2H), 2.93 (s, 3H);

APCI-MS m/z: 490.0 [MH^+].

Examples 45 to 55

The following compounds were synthesised using an analogous method to that described for Example 44.

Ex.	Compound	^{1}H NMR	m/z	SM
45	5-[(4-Cyanophenyl)sulfinyl]-*N*-(cyclopropylmethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.09 (s, 1H), 8.66 (d, J = 9.5 Hz, 1H), 7.88 - 7.76 (m, 6H), 7.51 (t, J = 2.1 Hz, 1H), 7.44 (t, J = 6.8 Hz, 1H), 3.22 (ddd, J = 7.1, 5.5, 1.8 Hz, 2H), 2.41 (d, J = 10.1 Hz, 3H), 1.00 - 0.91 (m, 1H), 0.47 (dt, J = 7.8, 5.0 Hz, 2H), 0.19 (dd, J = 14.7, 1.3 Hz, 2H)	500.1	SM25
46	*N*-Methyl-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.08 (q, J = 5.0 Hz, 1H), 8.78 (d, J = 2.6 Hz, 1H), 8.26 (d, J = 2.6 Hz, 1H), 8.10 (s, 1H), 7.97 - 7.89 (m, 2H), 7.86 - 7.72 (m, 3H), 7.66 - 7.53 (m, 3H), 2.76 (d, J = 4.8 Hz, 3H)	421.0	SM26

47	*N*-(Cyanomethyl)-5-[(4-cyanophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.51 (t, *J* = 5.8 Hz, 1H), 8.34 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 2H), 8.02 - 7.82 (m, 6H), 4.24 (d, *J* = 5.9 Hz, 2H), 2.36 (s, 3H)	485.0	SM25
48	5-[(4-Cyanophenyl)sulfinyl]-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.20 (t, *J* = 5.0 Hz, 1H), 8.94 (d, *J* = 1.1 Hz, 1H), 8.29 (d, *J* = 2.2 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 7.99 (d, *J* = 5.1 Hz, 6H), 7.89 (m, 1H), 7.40 (s, 2H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.35 (s, 3H)	540.1	SM25
49	5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxypropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.24 (t, *J* = 5.6 Hz, 1H), 8.32 (t, *J* = 1.7 Hz, 1H), 8.12 - 8.08 (m, 2H), 8.00 (d, *J* = 4.8 Hz, 1H), 7.96 - 7.80 (m, 5H), 4.77 - 4.73 (m, 1H), 3.68 - 3.62 (m, 1H), 3.13 - 3.01 (m, 1H), 2.35 (s, 3H), 0.99 (dd, *J* = 6.2, 2.0 Hz, 3H)	504.1	SM25
50	5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-(2-morpholin-4-ylethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.16 (t, *J* = 2.0 Hz, 1H), 8.30 (d, *J* = 2.6 Hz, 1H), 8.10 (dd, *J* = 8.5, 1.5 Hz, 2H), 8.01 (m, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.91 - 7.80 (m, 4H), 3.49 (t, *J* = 4.5 Hz, 4H), 3.34 (m, 2H), 2.38 - 2.32 (m, 9H)	559.1	SM25
51	5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxy-1,1-dimethylethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.30 (s, 1H), 8.67 (d, *J* = 17.3 Hz, 1H), 7.87 (dd, *J* = 8.4, 4.2 Hz, 3H), 7.49 (d, *J* = 10.1 Hz, 1H), 7.45 - 7.40 (m, 2H), 3.60 (d, *J* = 10.8 Hz, 2H), 3.61 (s, 2H), 2.41 (d, *J* = 6.7 Hz, 3H), 1.32 - 1.30 (m, 6H)	518.1	SM25

52	5-[(4-Cyanophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	8.98 (s, 1H), 8.65 (d, *J* = 12.6 Hz, 1H), 7.87 - 7.84 (m, 3H), 7.79 (m, 3H), 7.50 (d, *J* = 5.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 2.90 (dd, *J* = 4.8, 2.3 Hz, 3H), 2.42 (d, *J* = 7.8 Hz, 3H)	460.0	SM25
53	5-[(4-Cyanophenyl)sulfinyl]-*N*-[(2*R*)-2-hydroxypropyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.35 (s, 1H), 8.66 (d, *J* = 12.5 Hz, 1H), 7.88 - 7.81 (m, 3H), 7.81 - 7.77 (m, 3H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 8.7 Hz, 1H), 3.95 (m, 1H), 3.51 - 3.47 (m, 1H), 3.34 - 3.28 (m, 1H), 2.42 (d, *J* = 7.3 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H)	504.1	SM25
54	5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.15 (t,1H), 8.30 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 4.7 Hz, 1H), 7.95 - 7.81 (m, 5H), 3.31 - 3.23 (m, 3H), 3.19 - 3.11 (m, 3H), 2.35 (s, 3H), 2.14 (t, *J* = 8.1 Hz, 2H), 1.86 (q, *J* = 7.5 Hz, 2H), 1.61 (q, *J* = 6.9 Hz, 2H)	571.1	SM25
55	5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-methoxypropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.19 (t, *J* = 5.4 Hz, 1H), 8.33 - 8.31 (m, 1H), 8.13 - 7.78 (m, 8H), 3.48 - 3.31 (m, 2H), 3.29 - 3.11 (m, 4H), 2.34 (s, 3H), 1.00 (m, 3H)	518.0	SM25

Example 56

6-Methyl-5-(methylsulfonyl)-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

From the reaction using starting material SM5 in which Example 7 was isolated, the title sulfone was also isolated (8 mg).

^{1}H NMR (399.99 MHz, DMSO-d_6) δ 9.82 (t, J = 5.6 Hz, 1H), 8.99 (d, J = 2.0 Hz, 1H), 8.79 (s, 1H), 8.27 (dd, J = 8.2, 2.3 Hz, 1H), 8.00 (s, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.88 (t, J = 7.9 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 4.73 (d, J = 5.6 Hz, 2H), 3.29 (d, J = 1.6 Hz, 6H), 2.39 (s, 3H);

APCI-MS m/z: 544.0 (MH^+).

Examples 57 to 64

The following sulfone compounds were isolated from the previously described reactions yielding the corresponding sulfoxide compounds, or prepared analogously to Example 14.

Ex.	Compound	^{1}H NMR	m/z	SM
57	2-Oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-5-(phenylsulfonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.17 (t, J = 5.8 Hz, 1H), 8.83 (d, J = 2.9 Hz, 1H), 8.50 (d, J = 2.9 Hz, 1H), 8.06 (m, 3H), 7.91 (t, J = 9.1 Hz, 2H), 7.81 (t, J = 8.0 Hz, 1H), 7.74 (t, J = 7.4 Hz, 1H), 7.67 (t, J = 7.6 Hz, 2H), 3.29 (t, J = 7.0 Hz, 2H), 3.23 (q, J = 6.5 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H), 2.16 (t, J = 8.1 Hz, 2H), 1.87 (quintet, J = 7.5 Hz, 2H), 1.64 (quintet, J = 6.9 Hz, 2H)	548.1	SM2
58	5-[(4-Cyanophenyl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.25 (s, 1H), 8.70 (s, 1H), 8.06 (d, J = 8.6 Hz, 2H), 7.87 (dd, J = 14.6, 8.2 Hz, 3H), 7.77 (t, J = 7.9 Hz, 1H), 7.44 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 5.83 (s, 1H), 2.36 (s, 3H)	492.1	SM7

59	5-{[4-(Acetylamino)phenyl]-sulfonyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	10.42 (s, 1H), 9.63 (t, *J* = 6.1 Hz, 1H), 8.91 (s, 1H), 7.97 (s, 1H), 7.92 - 7.72 (m, 9H), 7.54 (d, *J* = 8.3 Hz, 2H), 4.59 (d, *J* = 6.2 Hz, 2H), 3.17 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H)	662.1	SM1
60	5-[(4-Ethylphenyl)sulfonyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.62 (t, *J* = 6.1 Hz, 1H), 8.91 (s, 1H), 7.98 (s, 1H), 7.92 - 7.75 (m, 7H), 7.58 - 7.47 (m, 4H), 4.59 (d, *J* = 5.8 Hz, 2H), 3.17 (s, 3H), 2.71 (q, *J* = 7.7 Hz, 2H), 2.23 (s, 3H), 1.20 (t, *J* = 7.5 Hz, 3H)	633.4	SM1
61	5-[(4-Cyanophenyl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.22 (s, 1H), 8.92 (d, *J* = 4.5 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.86 (dd, *J* = 13.0, 8.3 Hz, 3H), 7.76 (t, *J* = 7.9 Hz, 1H), 7.43 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 2.95 (d, *J* = 5.0 Hz, 3H), 2.37 (s, 3H)	476.0	SM24
62	5-[(4-Cyanophenyl)sulfonyl]-*N*-(2-hydroxy-1,1-dimethylethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.24 (d, *J* = 6.0 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.87 (dd, *J* = 15.0, 8.2 Hz, 3H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 3.66 (d, *J* = 6.2 Hz, 2H), 2.35 (s, 3H), 1.35 (d, *J* = 1.2 Hz, 6H)	534.1	SM22
63	*N*-[(3-Cyclopropylisoxazol-5-yl)methyl]-6-methyl-5-(methylsulfonyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.54 (t, *J*=6.1, 1H), 8.78 (s, 1H), 7.98 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.86 (t, *J*=7.8 Hz, 1H), 7.79 (d, *J*=7.8, 1H), 6.04 (s, 1H), 4.56 (d, *J*=6.2 Hz, 2H), 3.29 (s, 3H), 2.38 (s, 3H), 1.98-1.91 (m, 1H), 0.99-0.93 (m, 2H), 0.73-0.68 (m, 2H)	496.0	SM27

64	5-[(6-Cyanopyridin-3-yl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.25 (dd, J = 1.9, 0.4 Hz, 1H), 8.97 - 8.88 (m, 2H), 8.64 (dd, J = 8.2, 2.4 Hz, 1H), 8.33 (dd, J = 8.3, 0.7 Hz, 1H), 7.95 - 7.88 (m, 2H), 7.82 (t, J = 8.0 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H), 2.21 (s, 3H)	477.1	SM24

Example 65

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-({4-[(trimethylsilyl)ethynyl]phenyl}sulfinyl)-1,2-dihydropyridine-3-carboxamide

4-Bromobenzenethiol (177 mg, 1 mmol), tributylstannyl chloride (325 mg) and potassium carbonate (0.5 g) were mixed in acetonitrile and stirred overnight. The mixture was filtered and evaporated and the residue was dissolved in DMF (4 ml). 5-Iodo-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, starting material SM1 (590 mg) and bis(tri-*t*-butylphosphine)palladium (25 mg) were added. The mixture was degassed by bubbling argon through for 2 min, and was then heated in a microwave reactor at 150 °C for 15 min. The reaction mixture was partitioned between EtOAc and brine. The organic phase was filtered and evaporated to give a brown residue that was further purified by HPLC to afford the sulfide. The sulfide was dissolved in HOAc (2 ml). Hydrogen peroxide (0.5 ml of a 35% aq. solution) was added and the mixture heated to 50 °C for 30 min, whereupon the mixture was injected and purified on a HPLC, to yield 5-[(4-bromophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (60 mg).

5-[(4-Bromophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (180 mg) and DABCO (90 mg) were dissolved in DMF (10 ml). Ethynyl(trimethyl)silane (0.10 ml) was added followed by bis(tri-*tert*-butylphosphoranyl)palladium (40 mg). The reaction mixture was

stirred for 72 h and then partitioned between EtOAc and brine. The organic phase was evaporated and the residue purified by HPLC to yield the title compound (50 mg).
^{1}H NMR (299.946 MHz, DMSO-d_6) δ 9.64 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 2.0 Hz, 1H), 8.01 (d, J = 5.9 Hz, 1H), 7.93 (t, J = 3.5 Hz, 1H), 7.89 - 7.77 (m, 4H), 7.73 - 7.65 (m, 4H), 7.49 (d, J = 8.3 Hz, 2H), 4.61 - 4.45 (m, 2H), 3.15 (s, 3H), 2.33 (s, 3H), 0.24 (s, 9H);
APCI-MS m/z: 685.3.

Example 66

5-[(4-Ethynylphenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5-[(4-Bromophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, intermediate prepared in Example 65, (1.68 g, 2.5 mmol) and DABCO (1.4 g, 12.5 mmol) were dissolved in DMF (10 ml). Ethynyl(trimethyl)silane (0.80 ml) was added followed by bis(tri-*tert*-butylphosphoranyl)palladium (100 mg, 0.2 mmol). The reaction mixture was stirred at 50 °C for 3h and then poured onto crushed ice. The precipitate was collected and dried and further purified by column chromatography to provide 6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-({4-[(trimethylsilyl)ethynyl]phenyl}sulfinyl)-1,2-dihydropyridine-3-carboxamide. This material was dissolved in MeOH (30 ml) and caesium fluoride (0.5 g) was added. After 10 min the reaction mixture was diluted with EtOAc (30 ml) and filtered through silica (20 g). The solvent was removed and the residue purified by HPLC to give the title compound (475 mg).
^{1}H NMR (399.99 MHz, DMSO-d_6) δ 9.65 (t, J = 6.0 Hz, 1H), 8.38 (d, J = 1.9 Hz, 1H), 8.01 (s, 1H), 7.93 (d, J = 7.3 Hz, 1H), 7.89 - 7.77 (m, 4H), 7.74 - 7.68 (m, 4H), 7.50 (d, J = 8.1 Hz, 2H), 4.61 - 4.46 (m, 2H), 4.42 (s, 1H), 3.15 (s, 3H), 2.33 (s, 3H);
APCI-MS m/z: 613.3 (MH^+).

Example 67

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-{[4-(phenylethynyl)phenyl]sulfinyl}-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5-[(4-Ethynylphenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 66, 61 mg, 0.1 mmol), DABCO (100 mg) and iodobenzene (0.15 ml) were mixed in DMF (2 ml). Bis(tri-*tert*-butylphosphoranyl)palladium (25 mg) was added and the mixture stirred at 50 °C for 2 h, then filtered through silica (2 g). Evaporation of the solvents afforded an oily residue that was purified by HPLC to give the title compound (15 mg).

^{1}H NMR (399.99 MHz, DMSO-d_6) δ 9.66 (t, J = 5.9 Hz, 1H), 8.39 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.89 - 7.73 (m, 7H), 7.63 - 7.55 (m, 3H), 7.53 - 7.41 (m, 5H), 4.54 (dd, J = 14.1, 6.0 Hz, 2H), 3.15 (s, 3H), 2.35 (s, 3H);

APCI-MS m/z: 689.1 (MH^+).

Example 68

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-[(4-prop-1-yn-1-ylphenyl)sulfinyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

The title compound was made by a procedure analogous to that described in Example 67.

^{1}H NMR (399.99 MHz, DMSO-d_6) δ 9.66 (t, J = 5.9 Hz, 1H), 8.39 (d, J = 2.3 Hz, 1H), 8.02 (s, 1H), 7.93 (d, J = 7.1 Hz, 1H), 7.88 - 7.78 (m, 4H), 7.67 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 4.53 (td, J = 14.9, 9.2 Hz, 2H), 3.15 (s, 3H), 2.32 (s, 3H), 2.07 (s, 3H);

APCI-MS m/z: 627.2 (MH^+).

Example 69

5-[(5-Cyanopyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5-Iodo-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (SM24, 8.0 g) in dry acetonitrile (150 ml) was degassed with argon. 2,4-Dimethoxybenzyl thiol (*Synth. Commun.* 1998, 28, 3219-3233) (5.0 g), (±)-*trans*-1,2-diaminocyclohexane (3.1 g) and copper(I) iodide (0.35 g) were added in succession and the mixture was heated to reflux overnight under argon. After cooling to RT, the mixture was filtered through celite, the filtrate was concentrated and the residue was dissolved in DCM (500 ml) and washed with brine. The organics were dried (Na_2SO_4), filtered and

evaporated. The residue was purified by chromatography (SiO_2, DCM-heptane-ethyl acetate 1:2:1 to 1:1:2 gradient) to yield 5-[(2,4-dimethoxybenzyl)thio]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (8.13 g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (q, J = 4.8 Hz, 1H), 8.40 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.71 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 2.3 Hz, 1H), 6.46 (dd, J = 8.2, 2.4 Hz, 1H), 3.86 (s, 2H), 3.73 (s, 3H), 3.73 (s, 3H), 2.79 (d, J = 4.8 Hz, 3H), 1.78 (s, 3H).

APCI-MS m/z: 493.1 (MH^+).

5-[(2,4-Dimethoxybenzyl)thio]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (1.0 g) was dissolved in dry 1,2-dichloroethane (40 ml), trifluoroacetic acid (3 ml) was added and the mixture was heated to reflux overnight. The mixture was evaporated and then repeatedly re-evaporated with ethyl acetate (3 x 50 ml) to yield 5-mercapto-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide as a white solid which was used in subsequent steps without further purification.

APCI-MS m/z: 343.1 (MH^+).

5-Mercapto-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (690 mg) and 6-chloronicotinonitrile (277 mg) were taken in dioxane (30 ml), Cs_2CO_3 (650 mg) was added and the resulting mixture was stirred under argon at 40 °C overnight. The reaction mixture was concentrated, dissolved in DCM (100 ml) and washed with brine. The organics were dried (Na_2SO_4), filtered and evaporated. The residue was purified by HPLC to yield 5-[(5-cyanopyridin-2-yl)thio]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (530 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (q, J = 4.8 Hz, 1H), 8.87 (d, J = 1.4 Hz, 1H), 8.37 (s, 1H), 8.17 (dd, J = 8.5, 2.1 Hz, 1H), 7.99 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.49 (dd, J = 8.5, 0.7 Hz, 1H), 2.79 (d, J = 4.8 Hz, 3H), 2.15 (s, 3H).

APCI-MS m/z: 445.1 (MH^+).

5-[(5-Cyanopyridin-2-yl)thio]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (500 mg) was taken in acetic acid (6 ml), hydrogen

peroxide (33%, 1.5 ml) was added and the mixture was stirred at 50 °C. After 2 h the reaction mixture was chromatographed (HPLC) to yield the title sulfoxide (375 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (ddd, J = 7.1, 1.7, 0.4 Hz, 1H), 8.98 (d, J = 2.7 Hz, 1H), 8.67 (dd, J = 8.1, 1.6 Hz, 1H), 8.42 (d, J = 6.9 Hz, 1H), 8.24 (dtd, J = 8.2, 1.0, 0.1 Hz, 1H), 8.01 - 7.71 (m, 4H), 2.74 (d, J = 4.8 Hz, 3H), 2.35 (d, J = 1.1 Hz, 3H), APCI-MS m/z: 461.1 (MH^+).

Examples 70 to 76

The following compounds were synthesised using an analogous method to that described for Example 69.

Ex.	Compound	^{1}H NMR	m/z
70	6-({2-Methyl-5-(methylcarbamoyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}sulfinyl)nicotinamide	9.07 - 8.96 (m, 2H), 8.53 (dd, J = 8.1, 2.1 Hz, 1H), 8.43 (d, J = 6.7 Hz, 1H), 8.28 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.02 - 7.73 (m, 5H), 2.74 (d, J = 4.8 Hz, 3H), 2.36 (s, 3H)	479.0
71	5-[(5-Chloropyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.00 (s, J = 2.1 Hz, 1H), 8.76 (dd, J = 4.8, 2.1 Hz, 1H), 8.44 (d, J = 8.1 Hz, 1H), 8.30 (dd, J = 8.3, 1.8 Hz, 1H), 8.07 (dd, J = 8.4, 1.3 Hz, 1H), 8.01 - 7.72 (m, 4H), 2.75 (d, J = 4.8 Hz, 3H), 2.33 (d, J = 0.9 Hz, 3H)	499.9, 471.9
72	5-[(5-Bromopyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.00 (s, 1H), 8.82 (dd, J = 4.7, 2.0 Hz, 1H), 8.46 - 8.40 (m, 2H), 8.03 - 7.72 (m, 5H), 2.75 (d, J = 4.8 Hz, 3H), 2.33 (s, 3H)	515.9, 513.9

73	5-[(5-Cyanopyridin-2-yl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.64 (t, *J* = 6.1 Hz, 1H), 9.13 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.66 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.45 (d, *J* = 7.6 Hz, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 8.03 - 7.72 (m, 6H), 7.50 (d, *J* = 8.3 Hz, 2H), 4.53 (m, 2H), 3.16 (s, 3H), 2.36 (d, *J* = 0.9 Hz, 3H)	615.0
74	5-[(5-Bromopyrimidin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.21 (d, *J* = 4.5 Hz, 2H), 9.02 (q, *J* = 4.9 Hz, 1H), 8.69 (d, *J* = 10.1 Hz, 1H), 8.00 - 7.66 (m, 4H), 2.77 (d, *J* = 4.8 Hz, 3H), 2.27 (d, *J* = 1.4 Hz, 3H)	514.9, 516.9
75	5-[(6-Bromopyridazin-3-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.00 (q, *J* = 4.8 Hz, 1H), 8.51 (d, *J* = 6.9 Hz, 1H), 8.36 (d, *J* = 8.8 Hz, 1H), 8.19 (dd, *J* = 8.9, 1.0 Hz, 1H), 8.00 - 7.71 (m, 4H), 2.76 (d, *J* = 4.8 Hz, 3H), 2.33 (d, *J* = 1.6 Hz, 3H)	515.2, 517.1

Example 76

5-[(6-Cyanopyridin-3-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of 5-mercapto-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, intermediate described in Example 69, (690 mg), 5-chloropyridine-2-carbonitrile (277 mg) and ()-*trans*-1,2-diaminocyclohexane (118 mg) in dry acetonitrile (10 ml) was degassed with argon. Copper (I) iodide (95 mg) was added and the mixture was stirred overnight at 82 °C. The mixture was cooled to RT, filtered through celite, the filtrate was concentrated, the residue was dissolved in DCM (100 ml) and washed with brine. The organics were dried (Na_2SO_4), filtered and evaporated. The residue was purified by HPLC to yield 5-[(6-cyanopyridin-3-yl)thio]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (328 mg).

APCI-MS m/z: 445.1 (MH^+).

To 5-[(6-cyanopyridin-3-yl)thio]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (325 mg) in acetic acid (6 ml) was added hydrogen peroxide (33%, 1.5 ml) and the resulting mixture was stirred at 50 °C. After 90 min the reaction mixture was chromatographed (HPLC) to yield title compound (218 mg).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 2H), 8.40 (ddd, J = 7.8, 2.0, 0.4 Hz, 1H), 8.34 - 8.28 (m, 2H), 8.01 - 7.78 (m, 4H), 2.74 (dd, J = 4.8, 1.1 Hz, 3H), 2.34 (s, 3H);
APCI-MS m/z: 461.1 (MH^+).

Examples 77 to 78

The following compounds were synthesised using an analogous method to that described for Example 76.

Ex.	Compound	^{1}H NMR	m/z
77	5-[(5-Cyano-2-thienyl)-sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.03 (q, J = 4.8 Hz, 1H), 8.65 (d, J = 0.9 Hz, 1H), 8.09 (d, J = 4.1 Hz, 1H), 8.01 - 7.70 (m, 5H), 2.79 (d, J = 4.6 Hz, 3H), 2.22 (s, 3H)	466.3
78	5-(1*H*-Imidazol-2-ylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.72 (t, J = 6.1 Hz, 1H), 8.83 (d, J = 8.1 Hz, 1H), 8.01 - 7.70 (m, 7H), 7.54 (d, J = 8.3 Hz, 2H), 7.31 (s, 2H), 4.59 (m, 2H), 3.17 (s, 3H), 2.14 (d, J = 6.8 Hz, 3H)	579.0

Example 79

6-Methyl-5-[(methylamino)sulfonyl]-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

Benzyl thiol (124 mg) and tributylstannyl chloride (325 mg) were mixed in acetonitrile (50 ml) and stirred overnight, whereupon the mixture was filtered through a short column

of silica which was washed with DCM. Evaporation of the solvents afforded an oily residue which was dissolved in DMF (4 ml). 5-Iodo-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide starting material SM 1 (590 mg) was added, followed by bis(tri-*t*-butylphosphine)palladium (100 mg). The resulting mixture was degassed by passing argon through the solution (5 min) and then heated in a microwave reactor to 150 °C for 15 min. The reaction mixture was partitioned between EtOAc and brine. The organic phase was filtered and evaporated to yield a solid residue which was purified by recrystallisation from 2-propanol. The resulting crystalline material was dissolved in HOAc (50 ml). Water (5 ml) was added and chlorine gas bubbled through the solution for 1 min. To remove excess chlorine, argon was bubbled through for another 15 min and the reaction mixture was freeze dried to yield 2-methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-sulfonyl chloride, which was used in subsequent steps without further purification.

2-Methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-sulfonyl chloride (40 mg) was dissolved in a 2M solution of methylamine in THF (1 ml). After 10 min the mixture was evaporated to dryness and the residue purified by HPLC to afford the title compound (42 mg).
^{1}H NMR (399.99 MHz, DMSO-d_6) δ 9.70 (t, J = 6.1 Hz, 1H), 8.75 (s, 1H), 8.03 (s, 1H), 7.95 - 7.75 (m, 6H), 7.54 (d, J = 8.4 Hz, 2H), 4.59 (d, J = 6.1 Hz, 2H), 3.17 (s, 3H), 2.52 (d, J = 5.0 Hz, 3H), 2.30 (s, 3H);
APCI-MS m/z: 558.1 (MH^+).

Examples 80 to 85

The following compounds were synthesised using an analogous method to that described for Example 79.

Ex.	Compound	^{1}H NMR	m/z

80	5-(Anilinosulfonyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	10.51 (s, 1H), 9.62 (t, *J* = 6.0 Hz, 1H), 8.76 (s, 1H), 7.98 - 7.77 (m, 5H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.16 - 7.10 (m, 3H), 4.56 (d, *J* = 6.0 Hz, 2H), 3.17 (s, 3H), 2.18 (s, 3H)	620.1
81	6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-{[(2-morpholin-4-ylethyl)amino]sulfonyl}-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.76 (s, 1H), 9.70 (t, *J* = 5.6 Hz, 1H), 8.77 (s, 1H), 8.26 (s, 1H), 8.03 - 7.75 (m, 5H), 7.54 (d, *J* = 8.0 Hz, 2H), 4.58 (d, *J* = 6.0 Hz, 2H), 4.07 - 3.89 (m, 2H), 3.74 - 3.58 (m, 2H), 3.57 - 3.02 (m, 11H), 2.32 (s, 3H)	657.1
82	5-{[(2-Cyanoethyl)(methyl)-amino]sulfonyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.65 (s, 1H), 8.72 (s, 1H), 7.98 - 7.73 (m, 6H), 7.54 (d, *J* = 7.3 Hz, 2H), 4.58 (d, *J* = 4.1 Hz, 2H), 3.40 - 3.34 (m, 2H), 3.17 (s, 3H), 2.88 - 2.80 (m, 5H), 2.30 (s, 3H)	611.1
83	6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-{[(6-morpholin-4-ylpyridin-3-yl)amino]sulfonyl}-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	10.05 (s, 1H), 9.64 (s, 1H), 8.63 (s, 1H), 7.99 (s, 1H), 7.95 - 7.74 (m, 6H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.38 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.82 (d, *J* = 9.2 Hz, 1H), 4.56 (d, *J* = 5.9 Hz, 2H), 3.66 (t, *J* = 5.0 Hz, 4H), 3.51 - 3.26 (m, 4H), 3.17 (s, 3H), 2.16 (s, 3H)	706.1

84	6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-(morpholin-4-ylsulfonyl)-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.68 (t, J = 6.1 Hz, 1H), 8.66 (s, 1H), 8.03 (s, 1H), 7.98 - 7.80 (m, 5H), 7.54 (d, J = 8.4 Hz, 2H), 4.58 (d, J = 6.1 Hz, 2H), 3.67 (t, J = 4.5 Hz, 4H), 3.17 (s, 3H), 3.09 (dd, J = 14.1, 11.0 Hz, 4H), 2.33 (s, 3H)	614.1
85	6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-[(pyridin-3-ylamino)sulfonyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	10.88 (s, 1H), 9.62 (t, J = 6.3 Hz, 1H), 8.73 (s, 1H), 8.36 (td, J = 4.7, 1.7 Hz, 1H), 7.99 (s, 1H), 7.95 - 7.73 (m, 6H), 7.61 - 7.48 (m, 3H), 7.40 (dd, J = 13.0, 0.7 Hz, 1H), 4.56 (d, J = 6.1 Hz, 2H), 3.17 (s, 3H), 2.28 (d, J = 6.4 Hz, 3H)	621.1

Example 86

2-Methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-sulfonic acid

2-Methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-sulfonyl chloride, intermediate described in Example 79, (60 mg) was dissolved in THF (5 ml). Imidazole (100 mg) was added and after 10 min the mixture was evaporated to dryness and the residue purified by HPLC to afford the title compound (22 mg).

^{1}H NMR (299.946 MHz, DMSO-d_6) δ 9.84 (t, J = 6.1 Hz, 1H), 8.85 (s, 1H), 7.96 - 7.67 (m, 6H), 7.54 (d, J = 8.4 Hz, 2H), 4.58 (d, J = 6.1 Hz, 2H), 3.16 (s, 3H), 2.28 (d, J = 6.2 Hz, 3H);

APCI-MS m/z: 565.1 (MH^+).

Preparation of Starting Materials

The starting materials for the Examples 1 to 86 are either commercially available or are readily prepared by standard methods from known materials. For example, the following

reactions are illustrations, but not a limitation, of the preparation of some of the starting materials.

Starting material SM1

5-Iodo-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To an ice-cooled solution of 3-(trifluoromethyl)aniline (64.5 g, 0.40 mol) and triethylamine (60 ml) in acetone (700 ml) was added dropwise, ethyl 3-chloro-3-oxopropanoate (63.6 g, 0.42 mol) in acetone (50 ml). After the addition (approx. 30 minutes) stirring was continued at RT overnight. The solvents were removed and water (1200 ml) was added. The resulting precipitate was filtered off, thoroughly washed twice with water and then dried to afford ethyl 3-oxo-3-{[3-(trifluoromethyl)phenyl]amino}propanoate as yellow powder (109 g, 99%).

^{1}H NMR (399.99 MHz, $CDCl_3$): δ 9.52 (1H, s); 7.87 (1H, s); 7.78 (1H, d); 7.46 (1H, t); 7.39 (1H, d); 4.29 (2H, q); 3.50 (2H, s); 1.35 (3H, t);

APCI-MS m/z: 276.1 [MH^+].

To a solution of ethyl 3-oxo-3-{[3-(trifluoromethyl)phenyl]amino}propanoate (19.2 g, 70 mmol) and sodium methoxide (7.6 g, 140 mmol) in EtOH (250 ml) was added 4-methoxybut-3-en-2-one (90%) (7.72 g, 77 mmol). After the addition, the reaction mixture was refluxed for 2 h and then cooled. Water (50 ml) and 2M NaOH were added and the mixture was stirred at RT overnight. The organic solvents were removed and the reaction mixture was extracted (washed) with EtOAc. The water phases were acidified with hydrochloric acid to pH 3-4, an orange coloured precipitate appeared and was filtered off, washed with water and dried. Recrystallisation twice from heptane/EtOAc (4:1) afforded 6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid (12 g, 58%) as a white powder.

^{1}H NMR (399.99 MHz, $CDCl_3$): δ 13.68 (1H, s); 8.54 (1H, d); 7.86 (1H, d); 7.79 (1H, t); 7.55 (1H, brs); 7.48 (1H, d); 6.58 (1H, d); 2.16 (3H, s);

APCI-MS m/z: 298.1 [MH^+].

A mixture of 6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid (7.43 g, 25 mmol), HATU (10.5 g, 27.5 mmol), HOAT (3.75 g, 27.5 mmol) and DIPEA (14.2 ml, 82.5 mmol) in NMP (65 ml) was reacted for 1 h, then 4-methylsulphonylbenzyl amine hydrochloride (5.8 g, 26 mmol) was added. After 1 h, the reaction mixture was slowly poured into stirred ice water (1 L). A powder was formed, and the water mixture was acidified to pH 3 with citric acid (0.5 M), and stirring was continued for 1h. The precipitate was filtered off, washed with water and dried in vacuum overnight. Recrystallisation from EtOAc gave 8.1 g (70%) of 6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide.

^{1}H NMR (399.99 MHz, $CDCl_3$): δ 10.00 (1H, brt); 8.60 (1H, d); 7.88 (2H, d); 7.83 (1H, d); 7.76 (1H, t); 7.53 (3H, m); 7.46 (1H, d); 6.49 (1H, d); 4.68 (2H, m); 3.03 (3H, s); 2.10 (3H, s);

APCI-MS m/z: 465.1 [MH^+].

To a solution of 6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (200 mg, 0.43 mmol) in MeCN (1.5 ml) at RT and under argon, was added trifluoromethanesulfonic acid (1 ml) followed by *N*-iodosuccinimide (97 mg, 0.43 mmol). After 45 min, the reaction mixture was diluted with DCM, washed with aqueous $NaHCO_3$, with aqueous NaS_2O_4 and water, dried (Na_2SO_4), and evaporated to give the title compound SM1 (200 mg).

^{1}H NMR (399.99 MHz, $CDCl_3$): δ 9.85 (1H, brt); 8.90 (1H, d); 7.88 (2H, d); 7.76 (2H, m); 7.50 (2H, d); 7.48 (1H, s); 7.40 (1H, d); 4.65 (2H, m); 3.03 (3H, s); 2.32 (3H, s);

APCI-MS m/z: 591.0 [MH^+].

Starting material SM1 was used in the synthesis of the compounds of Examples: 3 ,4, 12, 13, 31, 32 ,33, 34, 35, 36, 37, 59, 60, 65 and 79.

Starting materials SM2 to SM 27

The following compounds were synthesised using analogous methods to those described for SM1.

	Compound	^{1}H NMR	m/z	SM in

SM2	5-Iodo-2-oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.43 (t, J = 5.9 Hz, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.38 (t, J = 2.7 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H), 7.91 - 7.73 (m, 3H), 3.35 - 3.13 (m, 6H), 2.17 (t, J = 8.2 Hz, 2H), 1.88 (quintet, J = 7.5 Hz, 2H), 1.66 (quintet, J = 6.9 Hz, 2H).	534.0	Ex. 2, 57
SM3	*N*-Cyclopropyl-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		1, 5, 8, 9, 24
SM4	*N*-{[5-(Cyclopropylsulfonyl)-pyridin-2-yl]methyl}-5-iodo-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	10.20 (brs, 1H), 9.04 (d, J =2.1 Hz, 1H), 8.80 (d, J=2.7 Hz, 1H), 8.15 – 8.10 (m, 1H), 7.82 (d, J = 2.7Hz, 1H), 7.79 (s, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 5.3, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 4.86 (d, J = 5.7 Hz, 2H), 2.50-2.42 (m, 1H), 1.42-1.34 (m, 2H), 1.12-1.03 (m, 2H)	604.2	6
SM5	5-Iodo-6-methyl-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	10.00 (t, J = 5.60 Hz, 1H), 8.98 (d, J = 1.84 Hz, 1H), 8.59 (s, 1H), 8.26 (dd, J = 8.25, 2.39 Hz, 1H), 7.94 – 7.72 (m, 4H), 7.56 (d, J = 8.25 Hz, 1H), 4.71 (d, J = 5.69 Hz, 2H), 3.28 (s, 3H), 2.21 (s, 3H)		7, 28, 38, 56

SM6	*N*-[(2S)-2-Hydroxypropyl]-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		10
SM7	5-Iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		11, 58
SM8	*N*-Cyclopropyl-1-(3,5-difluorophenyl)-5-iodo-6-methyl-2-oxo-1,2-dihydro-pyridine-3-carboxamide		431.0	14
SM9	*N*-{[5-(Ethylsulfonyl)pyridin-2-yl]methyl}-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	10.01 (t, J = 5.7 Hz, 1H), 8.93 (dd, J = 2.3, 0.6 Hz, 1H), 8.59 (s, 1H), 8.23 (dd, J = 8.3, 2.4 Hz, 1H), 7.95 - 7.72 (m, 4H), 7.57 (d, J = 16.8 Hz, 1H), 4.72 (d, J = 5.7 Hz, 2H), 3.37 (q, J = 9.2 Hz, 2H), 2.21 (s, 3H), 1.11 (t, J = 7.4 Hz, 3H)	605.9	15
SM10	1-(3,5-Difluorophenyl)-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-5-iodo-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide	Used directly in next step		16
SM11	1-(3,5-Dichlorophenyl)-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-5-iodo-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide	Used directly in next step		17

SM12	5-Iodo-*N*-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide		423.1	18
SM13	1-(3,5-Dichlorophenyl)-5-iodo-*N*,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide	Used directly in next step		19
SM14	1-(3,5-Difluorophenyl)-*N*-[2-(*1H*-imidazol-4-yl)ethyl]-5-iodo-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide	Used directly in next step		20
SM15	1-(3,5-Difluorophenyl)-5-iodo-6-methyl-*N*-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	Used directly in next step		21
SM16	1-(3,5-Difluorophenyl)-5-iodo-*N*,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide	Used directly in next step		22
SM17	5-Iodo-6-methyl-*N*-[(3-methylisoxazol-5-yl)methyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	9.75 (t, *J*=5.9 Hz, 1H), 8.58 (s, 1H), 7.93-7.87 (m, 2H), 7.82 (t, *J*=7.8 Hz, 1H), 7.73 (d, *J*=7.8 Hz, 1H), 6.15 (s, 1H), 4.57 (d, *J*=6.0 Hz, 2H), 2.21 (s, 3H), 2.17 (s, 3H)	518.0	23

SM18	*N*-[3-(*1H*-Imidazol-1-yl)propyl]-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		25
SM19	5-Iodo-6-methyl-2-oxo-*N*-[3-(*1H*-1,2,3-triazol-1-yl)-propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		26
SM20	*N*-[(1-Hydroxycyclopropyl)-methyl]-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		27
SM21	5-Iodo-*N*-(2-methoxyethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		29
SM22	*N*-(2-Hydroxy-2-methylpropyl)-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		30, 62

SM23	*N*-(2-Hydroxy-2-methylpropyl)-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		39, 41
SM24	5-Iodo-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxamide	Used directly in next step		40,42, 43,61, 64, 69
SM25	5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid		447.0	44, 45, 47,48, 49, 50, 51, 52, 53, 54, 55, 56
SM26	5-[(4-Cyanophenyl)sulfinyl]-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxylic acid	Used directly in next step		46
SM27	5-Iodo-6-methyl-*N*-[(3-cyclopropylisoxazol-5-yl)methyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.73 (t, *J*=5.9 Hz, 1H), 8.58 (s, 1H), 7.93-7.87 (m, 2H), 7.82 (t, *J*=7.8 Hz, 1H), 7.72 (d, *J*=7.8 Hz, 1H), 6.04 (s, 1H), 4.54 (d, *J*=6.0 Hz, 2H), 2.21 (s, 3H), 1.98-1.90 (m, 1H), 0.99-0.92 (m, 2H), 0.76-0.67 (m, 2H)	543.9	63

SM28

N-[4-(Cyclopropylsulfonyl)benzyl]-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

The title compound was prepared using a procedure analogous to that described for SM1.

^{1}H NMR ($CDCl_3$): δ 9.86 (1H, t, J 5.8 Hz); 8.90 (1H, s); 7.83-7.80 (3H, m); 7.75 (1H, t, J 7.8 Hz); 7.49-7.47 (3H, m); 7.40 (1H, d, J 7.8 Hz); 4.66 (2H, t, J 5.7 Hz); 2.42 (1H, m); 2.31 (3H, s); 1.32 (2H, m); 1.01 (2H, m);

APCI-MS m/z: 617 [MH^+].

Example 87

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylthio)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

Tributyl(phenylthio)stannane (400 mg, 1 mmol) and 5-iodo-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (SM1, 590 mg, 1 mmol) were dissolved in DMF (3 ml). Bis(tri-*t*-butylphosphine)palladium (50 mg, 0.1 mmol) was added and the mixture degassed by bubbling argon through the solution, whereupon it was heated in a microwave oven to 150 °C for 45 minutes. The reaction mixture was filtered and then directly applied to preparative HPLC. The appropriate fractions were pooled and freeze-dried to provide the title compound as a white solid (480 mg).

^{1}H-NMR (DMSO-d_6): δ 9.81 (t, J = 6.1 Hz, 1H), 8.36 (s, 1H), 8.04 (s, 1H), 7.97 - 7.76 (m, 5H), 7.53 (d, J = 8.4 Hz, 2H), 7.40 - 7.17 (m, 5H), 4.57 (d, J = 6.2 Hz, 2H), 3.17 (s, 3H), 2.20 (s, 3H);

APCI-MS m/z: 572.9 [MH^+].

Example 88

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylthio)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 87, 60 mg, 0.1 mmol) and sodium periodate (35 mg, 0.15 mmol) were mixed in methanol (10 ml) and

water (2 ml) was added. The mixture was stirred at 60 °C overnight. A second portion of sodium periodate (50 mg) was added and the mixture was stirred for 4h at 60 °C whereupon it was cooled, filtered through a short column of silica and evaporated. The pale yellow oily residue was subjected to preparative HPLC. The appropriate fractions were pooled and freeze-dried to provide the title compound as a white solid (9 mg).
^{1}H-NMR (DMSO-d_6): δ 9.66 (t, J = 5.9 Hz, 1H), 8.41 (d, J = 2.8 Hz, 1H), 8.07 - 7.43 (m, 13H), 4.63 - 4.44 (m, 2H), 3.15 (s, 3H), 2.34 (s, 3H);
APCI-MS m/z: 589.0 [MH^+].

Example 89

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylsulfonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylthio)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 87, 70 mg, 0.12 mmol) was dissolved in acetic acid (5 ml). Hydrogen peroxide (3 ml of 35% solution in water) was added and the mixture was stirred at 60 °C overnight. The reaction mixture was directly purified using semi-preparative HPLC. The appropriate fractions were pooled and freeze-dried to provide the title compound as a white solid (74 mg).
^{1}H-NMR (DMSO-d_6): δ 9.62 (t, J = 6.1 Hz, 1H), 8.92 (s, 1H), 8.01 - 7.51 (m, 13H), 4.59 (d, J = 6.1 Hz, 2H), 3.17 (s, 3H), 2.22 (s, 3H);
APCI-MS m/z: 604.9 [MH^+].

Example 90

6-Methyl-5-(methylsulfinyl)-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

Tributylstannyl chloride (334 mg, 1 mmol) and sodium methylthiolate (70 mg, 1 mmol) were mixed and stirred in acetonitrile (20 ml) overnight. The reaction mixture was filtered through a short column of silica. The filtrate was evaporated and the residue dissolved in DMF (3 ml). 5-Iodo-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (SM1, 590 mg, 1 mmol) and bis(tri-*t*-butylphosphine)palladium (50 mg, 0.1 mmol) were added and the mixture

degassed by bubbling argon through the solution, whereupon it was heated in a microwave oven to 150 °C for 45 minutes. The reaction mixture was filtered and then directly applied to preparative HPLC. The appropriate fractions were pooled and evaporated. This afforded 6-methyl-*N*-[4-(methylsulfonyl)benzyl]-5-(methylthio)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide as an off-white solid (377 mg). This material was pure enough for subsequent elaborations. The methylthio compound (51 mg, 0.1 mmol) and sodium periodate (70 mg, 0.3 mmol) were mixed in methanol (10 ml) and water (2 ml) was added. The mixture was stirred at 60 °C overnight, whereupon it was cooled, filtered through a short column of silica and evaporated. The residue was subjected to preparative HPLC. The appropriate fractions were pooled and freeze-dried to provide the title compound as a white solid (29 mg).

^{1}H-NMR (DMSO-d_6): δ 9.77 (t, J = 6.1 Hz, 1H), 8.78 (d, J = 1.3 Hz, 1H), 8.01 - 7.69 (m, 6H), 7.55 (d, J = 8.3 Hz, 2H), 4.63 - 4.58 (m, 2H), 3.17 (s, 3H), 2.78 (s, 1.4H), 2.77 (s, 1.6H), 2.08 (s, 1.4H), 2.08 (s, 1.6H);

APCI-MS m/z: 527.3 [MH^+].

Example 91

6-Methyl-5-(methylsulfonyl)-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

6-Methyl-5-(methylsulfinyl)-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 90, 51 mg, 0.1 mmol) was dissolved in acetic acid (5 ml). Hydrogen peroxide (3 ml of 35% solution in water) was added and the mixture was stirred at 60 °C overnight. The reaction mixture was directly purified using semi-preparative HPLC. The appropriate fractions were pooled and freeze-dried to provide the title compound as a white solid (32 mg).

^{1}H-NMR (DMSO-d_6): δ 9.63 (t, J = 6.1 Hz, 1H), 8.78 (s, 1H), 8.01 - 7.76 (m, 6H), 7.54 (d, J = 8.4 Hz, 2H), 4.59 (d, J = 6.1 Hz, 2H), 3.29 (s, 3H), 3.17 (s, 3H), 2.38 (s, 3H);

APCI-MS m/z: 542.9 [MH^+].

Example 92

5-(Benzylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

The title compound was prepared using a procedure analogous to that described for Example 90.

^{1}H-NMR (DMSO-d_6): δ 9.73 (t, J = 6.0 Hz, 1H), 8.60 (d, J = 4.4 Hz, 1H), 7.96 - 7.65 (m, 6H), 7.56 (d, J = 8.3 Hz, 2H), 7.41 - 7.19 (m, 5H), 4.60 (d, J = 6.0 Hz, 2H), 4.47 - 4.35 (m, 1H), 4.18 - 4.09 (m, 1H), 3.18 (s, 3H), 1.54 (s, 1.5H), 1.54 (s, 1.5H);

APCI-MS m/z: 603.4 [MH^+].

Example 93

5-(Ethylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

The title compound was prepared using a procedure analogous to that described for Example 90.

^{1}H-NMR (DMSO-d_6): δ 9.77 (t, J = 6.1 Hz, 1H), 8.69 (s, 1H), 8.01 - 7.74 (m, 6H), 7.55 (d, J = 8.4 Hz, 2H), 4.63 - 4.57 (m, 2H), 3.17 (s, 3H), 3.06 - 2.79 (m, 2H), 2.07 (s, 1.5H), 2.06 (s, 1.5H), 1.15 (t, J = 7.3 Hz, 3H);

APCI-MS m/z: 541.3 [MH^+].

Example 94

Methyl 3-({2-methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}sulfinyl)propanoate

The title compound was prepared using a procedure analogous to that described for Example 90.

^{1}H-NMR (DMSO-d_6): δ 9.76 (t, J = 6.1 Hz, 1H), 8.68 (s, 0.5H), 8.68 (s, 0.5H), 7.98 - 7.71 (m, 6H), 7.55 (d, J = 8.3 Hz, 2H), 4.63 - 4.57 (m, 2H), 3.60 (s, 1.5H), 3.59 (s, 1.5H), 3.27 - 3.01 (m, 5H), 2.84 - 2.61 (m, 2H), 2.06 (s, 3H);

APCI-MS m/z: 599.1 [MH^+].

Example 95

5-(Cyclohexylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

The title compound was prepared using a procedure analogous to that described for Example 90.

^{1}H-NMR (DMSO-d_6): δ 9.79 (t, J = 6.1 Hz, 1H), 8.64 (s, 1H), 8.06 - 7.75 (m, 6H), 7.55 (d, J = 8.1 Hz, 2H), 4.67 - 4.50 (m, 2H), 3.17 (s, 3H), 2.84 - 2.68 (m, 1H), 2.06 (s, 3H), 1.95 - 1.70 (m, 4H), 1.68 - 1.57 (m, 2H), 1.50 - 1.09 (m, 4H);

APCI-MS m/z: 595.1 [MH^+].

Example 96

5-(Cyclopropylsulfonyl)-N-[4-(cyclopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

a) Sodium cyclopropanesulfinate

The subtitle compound was obtained as a white solid, starting from cyclopropanesulfonyl chloride, using an analogous synthetic procedure to that described in Helvetica Chimica Acta, vol. 86 (2003), 65-81.

^{1}H NMR (CD_3OD): δ 1.87 (1H, tt, J 8.2, 5.0 Hz); 0.75 (2H, m; 0.61 (2H, m).

b) 5-(Cyclopropylsulfonyl)-N-[4-(cyclopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of N-[4-(cyclopropylsulfonyl)benzyl]-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (SM28, 180.4 mg, 0.29 mmol), copper(I) iodide (69.9 mg, 0.37 mmol), sodium cyclopropanesulfinate (Example 96a, 75.4 mg, 0.59 mmol) and DMF (2 ml) was stirred at 100 °C for 1 h. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by preparative HPLC to give the title compound as white solid (12 mg, 7 %).

^{1}H NMR ($CDCl_3$): δ 9.60 (1H, t, J 5.8 Hz); 9.09 (1H, s); 7.90 - 7.76 (4H, m); 7.53 (1H, s); 7.49 (2H, d, J 8.3 Hz); 7.44 (1H, d, J 8.0 Hz); 4.69 (2H, m); 2.60 (1H, m); 2.42 (1H, m); 1.44 (2H, m); 1.33 (2H, m); 1.18 (2H, m); 1.02 (2H, m); 2.54 (3H, s);
APCI-MS m/z: 595.4 [MH^+].

Human Neutrophil Elastase Quenched-FRET Assay

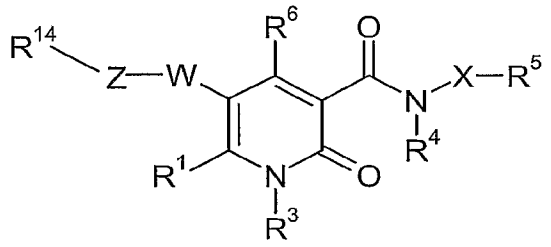
The assay uses Human Neutrophil Elastase (HNE) purified from serum (Calbiochem art. 324681; Ref. Baugh, R.J. et al., 1976, Biochemistry. 15, 836-841). HNE was stored in 50 mM sodium acetate (NaOAc), 200 mM sodium chloride (NaCl), pH 5.5 with added 30% glycerol at -20 °C. The protease substrate used was Elastase Substrate V Fluorogenic, MeOSuc-AAPV-AMC (Calbiochem art. 324740; Ref. Castillo, M.J. et al., 1979, Anal. Biochem. 99, 53-64). The substrate was stored in dimethyl sulphoxide (DMSO) at -20 °C. The assay additions were as follows: Test compounds and controls were added to black 96-well flat-bottom plates (Greiner 655076), 1 µL in 100% DMSO, followed by 30 µL HNE in assay buffer with 0.01% Triton (trade mark) X-100 detergent. The assay buffer constitution was: 100 mM Tris(hydroxymethyl)aminomethane (TRIS) (pH 7.5) and 500 mM NaCl. The enzyme and the compounds were incubated at room temperature for 15 minutes. Then 30 µl substrate in assay buffer was added. The assay was incubated for 30 minutes at room temperature. The concentrations of HNE enzyme and substrate during the incubation were 1.7 nM and 100 µM, respectively. The assay was then stopped by adding 60 µl stop solution (140 mM acetic acid, 200 mM sodium monochloroacetate, 60 mM sodium acetate, pH 4.3). Fluorescence was measured on a Wallac 1420 Victor 2 instrument at settings: Excitation 380 nm, Emission 460 nm. IC_{50} values were determined using Xlfit curve fitting using model 205.

When tested in the above screen, the compounds of the Examples gave IC_{50} values for inhibition of human neutrophil elastase activity of less than 30 µM (micromolar), indicating that the compounds of the invention are expected to possess useful therapeutic properties. Specimen results are shown in the following Table:

Compound of	Inhibition of Human Neutrophil Elastase IC_{50} (micromolar, μM)
Example 27	0.009
Example 49	0.004
Example 54	0.0005
Example 59	0.014
Example 86	0.045

CLAIMS

1. A compound of formula (I)



(I)

wherein

R^{1} represents hydrogen or C_1-C_6 alkyl;

W represents $S(O)_m$ wherein m represents an integer 0, 1 or 2;

Z represents a single bond, $-CH_2-$ or $-NR^{25}-$;

R^{14} represents a hydrogen atom or OH or a group selected from C_1-C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur; each group being optionally substituted with at least one substituent selected from phenyl, C_1-C_6 alkoxycarbonyl, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CN, OH, NO_2, C_1-C_3 alkyl substituted by one or more F atoms, C_1-C_3 alkoxy substituted by one or more F atoms, $NR^{12}R^{13}$, $C{\equiv}CR^{30}$, $CONR^{31}R^{32}$, CHO, C_2-C_4 alkanoyl, $S(O)_pR^{33}$ and OSO_2R^{34};

R^{12} and **R**^{13} independently represent H, C_1-C_6 alkyl, formyl or C_2-C_6 alkanoyl; or the group $-\mathbf{NR^{12}R^{13}}$ together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{26};

$\mathbf{R^{30}}$ represents H, C_1-C_3 alkyl, $Si(CH_3)_3$ or phenyl;

$\mathbf{R^{33}}$ and $\mathbf{R^{34}}$ independently represent H or C_1-C_3 alkyl; said alkyl being optionally substituted by one or more F atoms;

$\mathbf{R^6}$ represents H or F;

$\mathbf{R^3}$ represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said ring being optionally substituted with at least one substituent selected from halogen, C_1-C_6 alkyl, cyano, C_1-C_6 alkoxy, nitro, methylcarbonyl, $NR^{35}R^{36}$, C_1-C_3 alkyl substituted by one or more F atoms or C_1-C_3 alkoxy substituted by one or more F atoms;

$\mathbf{R^{35}}$ and $\mathbf{R^{36}}$ independently represent H or C_1-C_3 alkyl; said alkyl being optionally further substituted by one or more F atoms;

$\mathbf{R^4}$ represents hydrogen or C_1-C_6 alkyl optionally substituted with at least one substituent selected from fluoro, hydroxyl and C_1-C_6 alkoxy;

X represents a single bond, O, NR^{24} or a group -C_1-C_6 alkylene-Y-, wherein Y represents a single bond, oxygen atom, NR^{24} or $S(O)_w$; and said alkylene being optionally further substituted by OH, halogen, CN, $NR^{37}R^{38}$, C_1-C_3 alkoxy, $CONR^{39}R^{40}$, SO_2R^{41} and $SO_2NR^{42}R^{43}$;

or $\mathbf{R^4}$ and **X** are joined together such that the group –$\mathbf{NR^4X}$ together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from

O, S and NR^{44}; said ring being optionally substituted by C_1-C_6 alkyl or $NR^{45}R^{46}$; said alkyl being optionally further substituted by OH;

either $\mathbf{R^5}$ represents a monocyclic ring system selected from

i) phenoxy,

ii) phenyl,

iii) a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur,

iv) a saturated or partially unsaturated C_3-C_6 hydrocarbyl ring, or

v) a saturated or partially unsaturated 4- to 7-membered heterocyclic ring comprising at least one ring heteroatom selected from oxygen, $S(O)_r$ and NR^{20}, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group,

or $\mathbf{R^5}$ represents a bicyclic ring system in which the two rings are independently selected from the monocyclic ring systems defined in ii), iii), iv) and v) above, wherein the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group selected from oxygen, $S(O)_t$ or C_1-C_6 alkylene optionally comprising one or more internal or terminal heteroatoms selected from oxygen, sulphur and NR^{27} and being optionally substituted by at least one substituent selected from hydroxyl, oxo and C_1-C_6 alkoxy,

the monocyclic or bicyclic ring system being optionally substituted by at least one substituent selected from oxygen, CN, OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, $NR^{47}R^{48}$, NO_2, OSO_2R^{49}, CO_2R^{50}, $C(=NH)NH_2$, $C(O)NR^{51}R^{52}$, $C(S)NR^{53}R^{54}$, $SC(=NH)NH_2$, $NR^{55}C(=NH)NH_2$, $S(O)_vR^{21}$, $SO_2NR^{56}R^{57}$, C_1-C_3 alkoxy substituted by one or more F atoms and C_1-C_3 alkyl substituted by SO_2R^{58} or by one or more F atoms; said C_1-C_6 alkyl being optionally further substituted with at least one substituent selected from cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio and $-C(O)NR^{22}R^{23}$;

or $\mathbf{R^5}$ may also represent H;

$\mathbf{R^{20}}$ represents hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl or C_1-C_6 alkoxycarbonyl;

$\mathbf{R^{21}}$ represents hydrogen, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; said alkyl or cycloalkyl group being optionally further substituted by one or more substituents selected independently from OH, CN, C_1-C_3 alkoxy and $CONR^{59}R^{60}$;

$\mathbf{R^{37}}$ and $\mathbf{R^{38}}$ independently represent H, C_1-C_6 alkyl, formyl or C_2-C_6 alkanoyl;

$\mathbf{R^{47}}$ and $\mathbf{R^{48}}$ independently represent H, C_1-C_6 alkyl, formyl, C_2-C_6 alkanoyl, $S(O)_qR^{61}$ or $SO_2NR^{62}R^{63}$; said alkyl group being optionally further substituted by halogen, CN, C_1-C_4 alkoxy or $CONR^{64}R^{65}$;

$\mathbf{R^{41}}$ and $\mathbf{R^{61}}$ independently represent H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

p is 0, 1 or 2;
q is 0, 1 or 2;
r is 0, 1 or 2;
t is 0, 1 or 2;
w is 0, 1 or 2;
v is 0, 1 or 2;

$\mathbf{R^{22}}$, $\mathbf{R^{23}}$, $\mathbf{R^{24}}$, $\mathbf{R^{25}}$, $\mathbf{R^{26}}$, $\mathbf{R^{27}}$, $\mathbf{R^{31}}$, $\mathbf{R^{32}}$, $\mathbf{R^{39}}$, $\mathbf{R^{40}}$, $\mathbf{R^{42}}$, $\mathbf{R^{43}}$, $\mathbf{R^{44}}$, $\mathbf{R^{45}}$, $\mathbf{R^{46}}$, $\mathbf{R^{49}}$, $\mathbf{R^{50}}$, $\mathbf{R^{51}}$, $\mathbf{R^{52}}$, $\mathbf{R^{53}}$, $\mathbf{R^{54}}$, $\mathbf{R^{55}}$, $\mathbf{R^{56}}$, $\mathbf{R^{57}}$, $\mathbf{R^{58}}$, $\mathbf{R^{59}}$, $\mathbf{R^{60}}$, $\mathbf{R^{62}}$, $\mathbf{R^{63}}$, $\mathbf{R^{64}}$ and $\mathbf{R^{65}}$ each independently represent hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein R^{14} represents phenyl optionally substituted by one or two substituents independently selected from CN, F, Cl, Br, CF_3, NO_2 and C≡CH.

3. A compound according to Claim 1 or Claim 2, wherein Z represents a single bond.

4. A compound according to any one of Claims 1 to 3, wherein R^3 represents a phenyl group substituted with a trifluoromethyl substituent.

5. A compound according to any one of Claims 1 to 4, wherein R^5 represents phenyl or pyridinyl substituted by $-S(O)_vR^{21}$ wherein v represents the integer 2.

6. A compound according to any one of Claims 1 to 5, wherein R^5 represents H.

7. A compound of formula (I) as defined in Claim 1 selected from:

N-Cyclopropyl-5-[(4-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

2-Oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Bromophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(2,4-Dimethoxybenzyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-cyclopropyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-{[5-(Cyclopropylsulfonyl)pyridin-2-yl]methyl}-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-(methylsulfinyl)-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Cyclopropyl-5-[(3-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Cyclopropyl-5-[(2-methoxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[(2*S*)-2-hydroxypropyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(2-Cyanoethyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-cyclopropyl-1-(3,5-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-dichlorophenyl)-*N*-{[5-(ethylsulfonyl)pyridin-2-yl]methyl}-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-dichlorophenyl)-*N*,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-6-methyl-*N*-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-1-(3,5-difluorophenyl)-*N*,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-[(3-methylisoxazol-5-yl)methyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Cyclopropyl-5-[(4-hydroxyphenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethy)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[3-(1*H*-imidazol-1-yl)propyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-*N*-[3-(1*H*-1,2,3-triazol-1-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[(1-hydroxycyclopropyl)methyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

1-(3-Cyanophenyl)-5-[(4-cyanophenyl)sulfinyl]-6-methyl-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-methoxyethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxy-2-methylpropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Chlorophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-[(4-methylphenyl)sulfinyl]-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-[(4-nitrophenyl)sulfinyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-{[4-(trifluoromethyl)phenyl]sulfinyl}-1,2-dihydropyridine-3-carboxamide;

5-{[4-(Acetylamino)phenyl]sulfinyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Ethylphenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Fluorophenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-1-(3-methylphenyl)-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-ethyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Chlorophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Ethyl-5-[(4-fluorophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Fluorophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Bromophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxyethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(cyclopropylmethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-Methyl-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-(Cyanomethyl)-5-[(4-cyanophenyl)sulfinyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxypropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-*N*-(2-morpholin-4-ylethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-hydroxy-1,1-dimethylethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-[(2*R*)-2-hydroxypropyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-6-methyl-2-oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfinyl]-*N*-(2-methoxypropyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-(methylsulfonyl)-*N*-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

2-Oxo-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-5-(phenylsulfonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-{[4-(Acetylamino)phenyl]sulfonyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Ethylphenyl)sulfonyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(4-Cyanophenyl)sulfonyl]-*N*-(2-hydroxy-1,1-dimethylethyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

N-[(3-Cyclopropylisoxazol-5-yl)methyl]-6-methyl-5-(methylsulfonyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(6-Cyanopyridin-3-yl)sulfonyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-({4-[(trimethylsilyl)ethynyl]phenyl}sulfinyl)-1,2-dihydropyridine-3-carboxamide;

5-[(4-Ethynylphenyl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-{[4-(phenylethynyl)phenyl]sulfinyl}-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-[(4-prop-1-yn-1-ylphenyl)sulfinyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Cyanopyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-({2-Methyl-5-(methylcarbamoyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}sulfinyl)nicotinamide;

5-[(5-Chloropyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Bromopyridin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Cyanopyridin-2-yl)sulfinyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Bromopyrimidin-2-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(6-Bromopyridazin-3-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(6-Cyanopyridin-3-yl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[(5-Cyano-2-thienyl)sulfinyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-(1*H*-Imidazol-2-ylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-[(methylamino)sulfonyl]-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-(Anilinosulfonyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-{[(2-morpholin-4-ylethyl)amino]sulfonyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-{[(2-Cyanoethyl)(methyl)amino]sulfonyl}-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-{[(6-morpholin-4-ylpyridin-3-yl)amino]sulfonyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-5-(morpholin-4-ylsulfonyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-[(pyridin-3-ylamino)sulfonyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

2-Methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-sulfonic acid;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylthio)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylsulfinyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(phenylsulfonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-(methylsulfinyl)-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

6-Methyl-5-(methylsulfonyl)-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-(Benzylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-(Ethylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

Methyl 3-({2-methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}sulfinyl)propanoate;

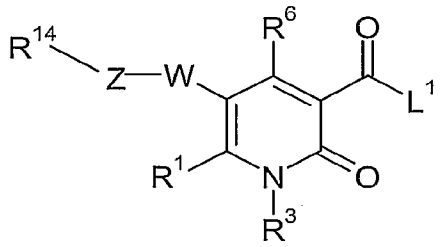
5-(Cyclohexylsulfinyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-(Cyclopropylsulfonyl)-N-[4-(cyclopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

and pharmaceutically acceptable salts of any one thereof.

8. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises,

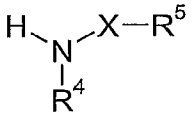
(a) reacting a compound of formula (II)



(II)

wherein L^1 represents a leaving group (such as halogen or hydroxyl) and R^1, R^3, R^6, R^{14}, W and Z are as defined in formula (I),

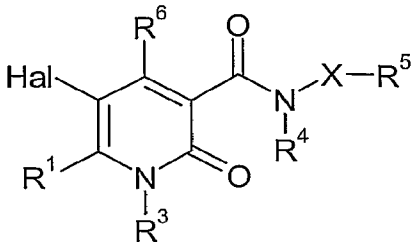
with a compound of formula



(III)

wherein X, R^4 and R^5 are as defined in formula (I); or

(b) when W represents –S– and Z represents a single bond or $–CH_2–$, reacting a compound of formula (IV)



(IV)

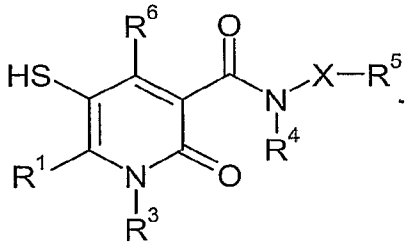
wherein Hal represents a halogen atom and X, R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with a nucleophile R^{14}–Z–S–M wherein R^{14} and Z are as defined in formula (I) and M represents an organo-tin or organo boronic acid group; or

(c) when W represents –S– and Z represents a single bond or $–CH_2–$, reacting a compound of formula (IV) wherein Hal represents a halogen atom and X, R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with a thiol R^{14}–Z–S–H wherein R^{14} and Z are as defined in formula (I) in the presence of a copper (I) salt; or

(d) when W represents –S– and Z represents a single bond or $–CH_2–$, reacting a compound of formula (V)

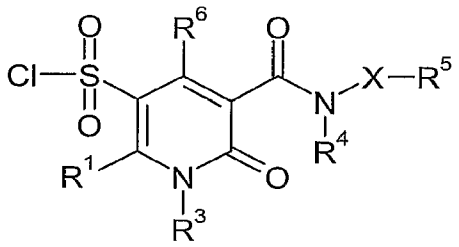


(V)

wherein X, R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with an electrophile R^{14}–Z–L^2 wherein L^2 represents a leaving group such as halogen and R^{14} and Z are as defined in formula (I); or

(e) when W represents –SO_2– and Z represents –NR^{25}–, reacting a compound of formula (VI)



(VI)

wherein X, R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with an amine R^{14}–NHR^{25} wherein R^{14} and R^{25} are as defined in formula (I); or

(f) when W represents a sulfinyl (–S(O) –) or a sulfonyl (–$S(O)_2$–) group, oxidising the corresponding compound wherein W represents a thio (–S –) group;

and optionally after (a), (b), (c), (d), (e) or (f) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

9. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt

thereof as claimed in any one of claims 1 to 7 with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A compound of formula (I) or a pharmaceutically-acceptable salt thereof as claimed in any one of claims 1 to 7 for use in therapy.

12. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of neutrophil elastase activity is beneficial.

13. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma, rhinitis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, cancer, atherosclerosis or gastric mucosal injury.

14. A method of treating, or reducing the risk of, a disease or condition in which inhibition of neutrophil elastase activity is beneficial which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 7.

15. A method of treating, or reducing the risk of, an inflammatory disease or condition which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 7.

16. A method according to Claim 14 or Claim 15, wherein the disease or condition is adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension,

asthma, rhinitis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, cancer, atherosclerosis or gastric mucosal injury.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000328

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004043924 A1 (ASTRAZENECA AB), 27 May 2004 (27.05.2004) --	1-16
A	WO 2005021509 A1 (ASTRAZENECA), 10 March 2005 (10.03.2005) --	1-16
A	WO 2004020410 A2 (BAYER HEALTHCARE AG), 11 March 2004 (11.03.2004) --	1-16
A	EP 1357111 A1 (SHIONOGI & CO., LTD.), 29 October 2003 (29.10.2003) --	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2006	21-06-2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/MP Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000328

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14-16
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 14-16 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 2005026123 A1 (ASTRAZENECA AB), 24 March 2005 (24.03.2005)	1-16
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P,A	WO 2005026124 A1 (ASTRAZENECA AB), 24 March 2005 (24.03.2005)	1-16
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International patent classification (IPC)

C07D 213/82 (2006.01)
A61K 31/4412 (2006.01)
A61K 31/4427 (2006.01)
A61K 31/444 (2006.01)
A61P 11/00 (2006.01)
A61P 11/06 (2006.01)
A61P 29/00 (2006.01)
C07D 213/83 (2006.01)
C07D 401/12 (2006.01)
C07D 409/12 (2006.01)
C07D 413/12 (2006.01)

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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

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